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(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: NAKAI, Kazuo [JP/JP]; 4-12-21-401, Sumie, Sumiyoshi-ku, Osaka-shi, Osaka 558 (JP). OGAWA, Yasuhiro [JP/JP]; 2-2-10, Midorigaoka, Ikeda-shi, Osaka 563 (JP). YAMADA, Akira [JP/JP]; 4-8-30, Sawada, Fujiidera-shi, Osaka 583 (JP). CHIBA, Toshiyuki [JP/JP]; 1-1-503, Nakatsujicho, Nara-shi, Nara 630 (JP). TAKASUGI, Hisashi [JP/JP]; 3-116-10, Mozu Umekita, Sakai-shi, Osaka 591 (JP).

(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

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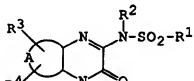
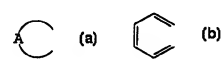
(54) Title: QUINOXALINE DERIVATIVES AS GLUTAMATE RECEPTOR ANTAGONISTS

(57) Abstract

The present invention relates to a novel condensed heterocyclic compound of formula (I) wherein R^1 is alkyl, etc.; R^2 is hydrogen, etc.; R^3 and R^4 are each independently hydrogen, etc.; a group of formula (a) is the group of formula (b), etc.; and a pharmaceutically acceptable salt thereof, which is useful as a medicament; the processes for the preparation of said condensed heterocyclic compound or a salt thereof; a pharmaceutical composition comprising said condensed heterocyclic compound or a pharmaceutical acceptable salt thereof; etc.



(I)



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DESCRIPTION

QUINOXALINE DERIVATIVES AS GLUTAMATE RECEPTOR ANTAGONISTS.

TECHNICAL FIELD

The present invention relates to a novel condensed heterocyclic compound and a salt thereof which are useful as a medicament.

BACKGROUND ART

Some glutamate receptor antagonists are known (e.g. WO 92/07847, etc).

DISCLOSURE OF INVENTION

The present invention relates to novel condensed heterocyclic compound and a salt thereof.

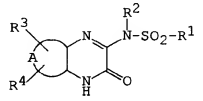
The condensed heterocyclic compound and a salt thereof of the present invention are the excitatory amino acid receptor antagonists, therefore, they possess glutamate receptor antagonism, in particular, 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA) receptor antagonism, and N-methyl-D-aspartate (NMDA) receptor antagonism.

The condensed heterocyclic compound or a salt thereof of the present invention is useful for the prevention and/or the treatment of anxiety, depression, schizophrenia, epilepsy, cognition disorders, stroke, cerebral ischemia, head trauma, spinal cord trauma, cardiac arrest, hypoglycemia, anoxia, convulsion, brain edema, Alzheimer's disease, Huntington's chorea, Parkinson's disease, opiate tolerance and withdrawal, or the like.

Accordingly, the objects of the present invention are to provide such potent condensed heterocyclic compound and a salt thereof; to provide a pharmaceutical composition comprising said condensed heterocyclic compound or a salt

thereof, as an active ingredient; to provide a method for the prevention and/or the treatment of aforesaid diseases in a human being or an animal; and the like.

The object condensed heterocyclic compound can be represented by the formula (I) :



(I)

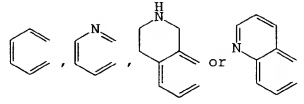
wherein R^1 is alkyl, halo(lower)alkyl, amino, aryl or heterocyclic group,

R^2 is hydrogen or lower alkyl,

R^3 and R^4 are each independently hydrogen, cyano, nitro, halogen, lower alkyl, halo(lower)alkyl, lower alkoxy, halo(lower)alkoxy, di(lower)-alkylamino, aryl which may have one or more substituent(s), heterocyclic group which may have one or more substituent(s), lower alkylthio which may have one or more substituent(s), heterocyclicthio, lower alkylsulfonyl, lower alkylaminosulfonyl, or heterocyclicsulfonyl,

a group of the formula :

is the group of the formula :



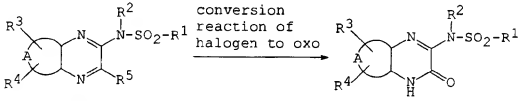
It is to be noted the object compound (I) may include one or more stereoisomers due to asymmetric carbon atom(s) and double bond, and all of such isomers and a mixture thereof are included within the scope of the present invention.

It is further to be noted isomerization or rearrangement of the object compound (I) may occur due to the effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention.

It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc) and any form of the crystal of the compound (I) are included within the scope of the present invention.

The object compound (I) or a salt thereof can be prepared according to the following reaction schemes.

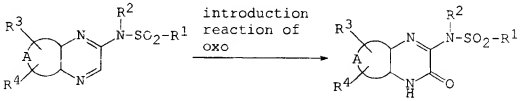
Process 1



(II)
or a salt thereof

(I)
or a salt thereof

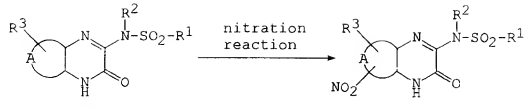
Process 2



(III)
or a salt thereof

(I)
or a salt thereof

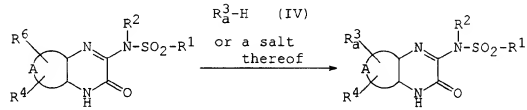
Process 3



(Ia) or a salt thereof

(Ib) or a salt thereof

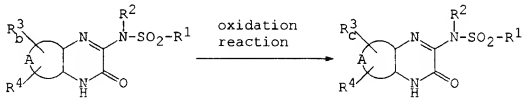
Process 4



(V) or a salt thereof

(Ic) or a salt thereof

Process 5



(Id) or a salt thereof

(Ie) or a salt thereof

wherein R^1, R^2, R^3, R^4 and a group of the formula :

are each as defined above,

R_a^3 is di(lower)alkylamino, N-containing heterocyclic group which may have one or more substituent(s), lower alkylthio which may have one or more substituent(s), or heterocyclicthio,

R_b^3 is lower alkylthio or heterocyclicthio,

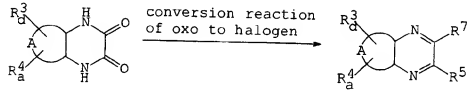
R_c^3 is lower alkylsulfonyl or heterocyclicsulfonyl,

R^5 is halogen, and

R^6 is a leaving group.

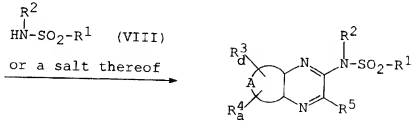
The starting compounds (II), (III) and (V) are novel, and they can be prepared, for example, according to the following reaction schemes.

Process A



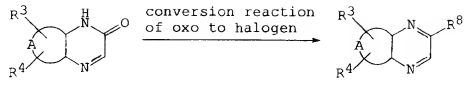
(VI)
or a salt thereof

(VII)
or a salt thereof



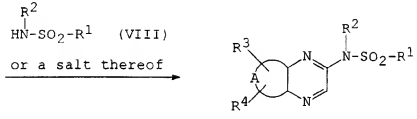
(IIa)
or a salt thereof

Process B



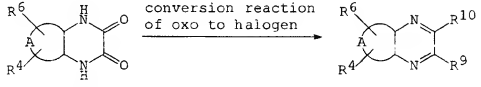
(IX)
or a salt thereof

(X)
or a salt thereof



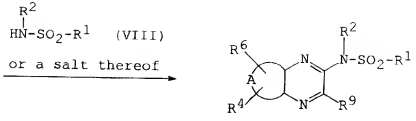
(III)
or a salt thereof

Process C

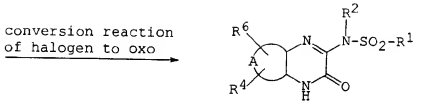


(XI)
or a salt thereof

(XII)
or a salt thereof



(XIII)
or a salt thereof



(V)
or a salt thereof

wherein R^1, R^2, R^3, R^4, R^5, R^6 and a group of the formula :

are each as defined above,

R_d^3 and R_a^4 are each independently hydrogen, nitro or halogen, and

R^7, R^8, R^9 and R^{10} are each halogen.

Suitable salts of the object compound (I) are pharmaceutically acceptable salts and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc), an ammonium salt, an organic base

salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc), an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc), and the like.

In the above and following descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

The term "higher" is intended to mean 7 to 20 carbon atoms unless otherwise indicated.

Suitable "alkyl" may include lower alkyl and higher alkyl.

Suitable example of "lower alkyl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl or the like, in which the preferred one may be (C_1-C_4)alkyl, and the more preferred one may be methyl, ethyl, propyl, isopropyl, and butyl.

Suitable "higher alkyl" may include straight or branched ones such as heptyl, 2-methylheptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, 11-methyldodecyl, 12-methyltridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl or the like, in which the preferred one may be (C_7-C_{16})alkyl, and the more preferred one may be octyl.

Suitable "aryl" may include phenyl, naphthyl, anthryl,

and the like, in which the preferred one may be (C_6-C_{10})aryl, and the more preferred one may be phenyl.

Said "aryl" may have one or more (preferably 1 to 3) substituent(s) such as nitro, or the like.

Suitable "heterocyclic group" and "heterocyclic" moiety in the terms of "heterocyclicthic" and "heterocyclicsulfonyl" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azepinyl (e.g. 1H-azepinyl, etc), pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc) etc;

saturated 3 to 8-membered (more preferably 5 to 7-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, perhydroazepinyl (e.g. perhydro-1H-azepinyl, etc), pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, quinoxalinyl, imidazopyridyl [e.g. imidazo[4,5-c]pyridyl, etc], tetrahydroimidazopyridyl [e.g. 4,5,6,7-tetrahydro[4,5-c]pyridyl, etc], etc;

saturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.2]nonanyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl,

isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc), etc;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc), dihydrothiazinyl, etc;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc;

saturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), and

saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl,

etc;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc; or the like.

Suitable "N-containing heterocyclic group" may be the ones as exemplified for aforesaid "heterocyclic group" which contains at least one nitrogen atom.

Aforesaid "heterocyclic group" and "N-containing heterocyclic group" may have one or more (preferably 1 to 3) substituent(s) such as lower alkyl, oxo, nitro, amino, aryl(lower)alkoxy which may have one or more substituent(s) [preferably, phenyl(lower)alkoxy which may have 1 to 3 lower alkoxy], hydroxy, halogen, aryl, or the like.

Suitable "halogen" may include fluoro, chloro, bromo and iodo.

Suitable "halo(lower)alkyl" may include mono- or di- or tri-halo(lower)alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl, 1,2-dibromoethyl, 3,3-dichloro-2-fluoropropyl, 2-iodobutyl, 4-trifluorobutyl, 1-chloro-3-fluoropentyl, 2,2-difluoro-6-chlorohexyl, in which the preferred one may be trihalo(lower)alkyl, the more preferred one may be trihalo(C_1-C_4)alkyl, and the most preferred one may be trifluoromethyl.

Suitable "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, hexyloxy, and the like, in which the preferred one may be (C_1-C_4)alkoxy and the more preferred one may be methoxy.

Suitable "halo(lower)alkoxy" may include mono- or di- or tri-halo(lower)alkoxy such as fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2-chloroethoxy, 1,2-dibromoethoxy, 3,3-dichloro-2-fluoropropoxy, 2-iodobutoxy, 4,4,4-trifluorobutoxy, 1-chloro-3-fluoropentyloxy, 2,2-difluoro-6-chlorohexyloxy, in which the preferred one may be trihalo(lower)alkoxy, the more preferred one may be trihalo(C_1-C_4)-

alkoxy, and the most preferred one may be trifluoromethoxy.

Suitable "lower alkylaminosulfonyl" may include mono- or di-(lower)alkylaminosulfonyl such as methylaminosulfonyl, dimethylaminosulfonyl, ethylaminosulfonyl, diethylaminosulfonyl, N-ethylpropylaminosulfonyl, butylaminosulfonyl, dibutylaminosulfonyl, N-pentyl-hexylaminosulfonyl, or the like, in which the preferred one may be di(lower)alkylaminosulfonyl, the more preferred one may be di(C_1-C_4)alkylaminosulfonyl, and the most preferred one may be dimethylaminosulfonyl.

Suitable "lower alkylsulfonyl" may include methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, t-butylsulfonyl, pentylsulfonyl, hexylsulfonyl, and the like, in which the preferred one may be (C_1-C_4)alkylsulfonyl, and the more preferred one may be methylsulfonyl.

Suitable "lower alkylthio" may include methylthio, ethylthio, propylthio, butylthio, t-butylthio, pentylthio, hexylthio, in which the preferred one may be (C_1-C_4)-alkylthio, and the more preferred one may be methylthio and ethylthio.

Said "lower alkylthio" may have one or more (preferably 1 to 3) substituent(s) such as di(lower)alkylamino as explained below, protected amino [preferably, acylamino; more preferably, lower alkanoylamino (e.g. formylamino, acetylamino, propionylamino, etc)], carboxy, or the like.

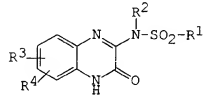
Suitable "di(lower)alkylamino" may include dimethylamino, diethylamino, N-ethylpropylamino, dibutylamino, N-pentyl-hexylamino, or the like, in which the preferred one may be di(C_1-C_4)alkylamino, and the more preferred one may be dimethylamino.

Suitable "a leaving group" may include halogen (e.g. fluoro, chloro, bromo, iodo), acyloxy such as lower alkanoyloxy (e.g. acetoxy, propionyloxy, etc), sulfonyloxy (e.g. methylsulfonyloxy, p-tolylsulfonyloxy, etc), and the

like.

Among the afore-mentioned condensed heterocyclic compound (I),

(A-1) one of the preferred one may be the compound of the formula (I-A)



(I-A)

wherein R^1, R^2, R^3 and R^4 are each as defined above, or a salt thereof,

(A-2) in which the more preferred one may be the compound of the formula (I-A)

wherein R^1 is lower alkyl, higher alkyl, tri-halo(lower)alkyl, amino, phenyl, or unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

R^2 is hydrogen or lower alkyl,

R^3 and R^4 are each independently hydrogen; cyano; nitro; halogen; lower alkyl; tri-halo(lower)alkyl; lower alkoxy; tri-halo(lower)alkoxy; di(lower)alkylamino; phenyl which may have 1 to 3 nitro; unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) or saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), each of which may have 1 to 3 substituent(s) selected from the group consisting of

lower alkyl, oxo, nitro, amino, phenyl(lower)alkoxy which may have 1 to 3 lower alkoxy, hydroxy, halogen and phenyl; lower alkylthio which may have 1 to 3 substituent(s) selected from the group consisting of di(lower)alkylamino, protected amino and carboxy; heterocyclicthio, in which heterocyclic moiety is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s); lower alkylsulfonyl; lower alkylaminosulfonyl; or heterocyclicsulfonyl, in which heterocyclic moiety is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

(A-3) the still more preferred one may be the compound of the formula (I-A)

wherein R^1 is lower alkyl, higher alkyl, tri-halo(lower)alkyl, amino, phenyl, or pyridyl,

R^2 is hydrogen or lower alkyl,

R^3 and R^4 are each independently hydrogen; cyano; nitro; halogen; lower alkyl; tri-halo(lower)alkyl; lower alkoxy; tri-halo(lower)alkoxy; di(lower)alkylamino; phenyl which may have 1 to 3 nitro; imidazolyl, dihydropyridyl or piperazinyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, oxo, nitro, amino, phenyl(lower)alkoxy which may have 1 to 3 lower alkoxy, hydroxy, halogen and phenyl; lower alkylthio which may have 1 to 3

substituent(s) selected from the group consisting of di(lower)alkylamino, lower alkanoylamino and carboxy; pyridylthio; imidazolylthio; lower alkylsulfonyl; di(lower)alkylaminosulfonyl; or imidazolylsulfonyl,

(A-4) the most preferred one may be the compound of the formula (I-A)

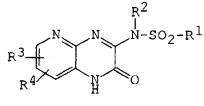
wherein R^1 is lower alkyl,

R^2 is hydrogen,

R^3 is hydrogen; imidazolyl; or dihydropyridyl which may have 1 to 3 substituent(s) selected from the group consisting of oxo, nitro, amino, lower alkyl, hydroxy, halogen and phenyl,

R^4 is nitro,

(B-1) another of the preferred one may be the compound of the formula (I-B)



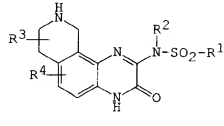
(I-B)

wherein R^1 is lower alkyl,

R^2 is hydrogen,

R^3 and R^4 are each nitro,

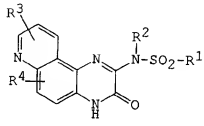
(C-1) another of the preferred one may be the compound of the formula (I-C)



(I-C)

wherein R^1 is lower alkyl,
R^2 is hydrogen,
R^3 is lower alkyl, and
R^4 is nitro,

(D-1) another of the preferred one may be the compound of the formula (I-D)



(I-D)

wherein R^1 is lower alkyl,
R^2 and R^3 are each hydrogen,
R^4 is nitro.

In the following, the processes for the preparation of the condensed heterocyclic compound (I) or a salt thereof are explained in detail.

Process 1

The compound (I) or a salt thereof can be prepared by subjecting the compound (II) or a salt thereof to conversion reaction of halogen to oxo.

Suitable salts of the compound (II) can be referred to those as exemplified for the compound (I).

This reaction can be carried out by reacting the compound (II) or a salt thereof with an acid such as acetic acid, trifluoroacetic acid, or the like.

This reaction can be carried out in a suitable solvent which does not adversely affect the reaction such as N,N-dimethylformamide, 1,3-dimethyl-2-imidazolidinone, or the like.

The reaction temperature is not critical, and the

reaction can be carried out at room temperature, under warming or under heating.

In case of using Lewis acid, the reaction may be carried out in the presence of a cation trapping agent (e.g. anisole, etc).

Process 2

The compound (I) or a salt thereof can be prepared by subjecting the compound (III) or a salt thereof to introduction reaction of oxo.

Suitable salts of the compound (III) can be referred to those as exemplified for the compound (I).

This reaction can be carried out by reacting the compound (III) or a salt thereof with a peroxy-acid such as monoperoxyphthalic acid, m-chloroperbenzoic acid, or the like.

The reaction can be carried out in a suitable solvent which does not adversely affect the reaction such as an acid (e.g. acetic acid, etc), or the like.

The reaction temperature is not critical, and the reaction can be carried out under warming to heating.

Process 3

The compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to nitration reaction.

Suitable salts of the compound (Ia) can be referred to those as exemplified for the compound (I).

This reaction can be carried out by reacting the compound (Ia) or a salt thereof with nitric acid or a salt thereof (e.g. potassium nitrate, etc), or the like.

The reaction can be preferably carried out in the presence of an acid (e.g. sulfuric acid, etc).

The reaction temperature is not critical, and the reaction can be carried out at room temperature, under

warming to heating.

Process 4

The compound (Ic) or a salt thereof can be prepared by reacting the compound (V) or a salt thereof with the compound (IV) or a salt thereof.

Suitable salts of the compounds (IV) and (V) can be referred to an acid addition salt as exemplified for the compound (I).

This reaction may be carried out in the presence of a base (e.g. sodium hydroxide, potassium hydroxide, etc).

This reaction can be carried out in a suitable solvent which does not adversely affect the reaction such as N,N-dimethylformamide, 1,3-dimethyl-2-imidazolidinone, dimethylsulfoxide, or the like.

The reaction temperature is not critical, and the reaction can be carried out under warming or under heating.

Process 5

The compound (Ie) or a salt thereof can be prepared by subjecting the compound (Id) or a salt thereof to oxidation reaction.

Suitable salts of the compounds (Id) and (Ie) can be referred to an acid addition salt as exemplified for the compound (I).

This reaction can be carried out by reacting the compound (Id) or a salt thereof with peroxy-acid such as hydrogen peroxide, m-chloroperbenzoic acid, or the like.

This reaction may be carried out in the presence of an acid such as acetic acid, hydrochloric acid, or the like.

The reaction temperature is not critical, and the reaction can be carried out at room temperature, under warming or under heating.

The reactions of Processes 1 to 5 can be carried out according to other methods than those as explained concretely

above.

The other methods than those of Processes 1 to 5 may be necessary for preparing the compound (I), but a person skilled in this art can carry out said methods, for example, with reference to Preparations and Examples described in this specification.

As for the preparation of the starting compounds, the reactions of Processes A to C can be carried out according to the methods described in Preparations in this specification or the known methods in this art.

Biological Property of the Compound (I)

In order to show the usefulness of the object compound (I), the biological test data of the representative compound of the compound (I) is shown in the following.

[^{3}H]AMPA binding assay

[I] Test Method

Rat cortical membrane suspension was incubated with [^{3}H]AMPA and test compound in 30 mM Tris-HCl buffer for 2 hours at 25°C. Incubation was terminated by rapid filtration under vacuum using Whatman GF/C filters then washed with Tris-HCl buffer. The radioactivity on the filter was measured using a liquid scintillation counter. Non-specific binding was terminated in the presence of 1 mM glutamate.

[II] Test Compound

3-Methylsulfonylamino-6,7-dinitro-2(1H)-quinoxalinone (the compound of Example 16)

[III] Test Result

IC_{50} value < 1 μM

Nephrotoxicity

[I] Test Method

Twenty-four hours after i.v. injection of test compound, mice were sacrificed, and blood samples and kidneys were taken. The weight of kidneys and the BUN (blood urea nitrogen) level in plasma were measured.

[II] Test Compound

6-(1-Imidazolyl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (the compound of Example 19)

[III] Test Result

In mice treated with test compound up to 100 mg/kg, the weight of kidneys and the BUN level were not significantly different from those for saline-treated animals.

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the object compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous, intramuscular and intra-articular) administrations or insufflation.

The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. And, if necessary, in addition, auxiliary, stabilizing, thickening and coloring agents and perfumes may be used.

The object compound (I) or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the diseases.

The pharmaceutical composition of the present invention can be manufactured by the conventional method in this field of the art. If necessary, the technique generally used in this field of the art for improving the bioavailability of a drug can be applied to the pharmaceutical composition of the present invention.

For applying the composition to a human being or an animal, it is preferable to apply it by intravenous (including i.v. infusion), intramuscular, pulmonary, or oral administration, or insufflation including aerosols from metered dose inhalator, nebulizer or dry powder inhalator.

While the dosage of therapeutically effective amount of the object compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.001-100 mg of the object compound (I) per kg weight of a human being or an animal, in the case of intramuscular administration, a daily dose of 0.001-100 mg of the object compound (I) per kg weight of a human being or an animal, in case of oral administration, a daily dose of 0.001-200 mg of the object compound (I) per kg weight of a human being or an animal is generally given for the prevention and/or the treatment of aforesaid diseases in a human being or an animal.

The following preparations and examples are given only for the purpose of illustrating the present invention in more detail.

Preparation 1

Methanesulfonyl chloride (7.74 ml) was added dropwise to a mixture of 40% aqueous methylamine solution (15.53 ml) and water (40 ml) at 0-5°C, and the reaction mixture was stirred at 0-5°C under nitrogen atmosphere for one hour. The aqueous mixture was extracted with two 150 ml portions of ethyl acetate, and the extract was dried over magnesium sulfate and evaporated to give N-methylmethanesulfonamide (7.72 g) as an oily product.

IR (Neat) : 1309 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.57 (s, 3H), 2.86 (s, 3H)

APCI-MS (m/z) : 110 (MH^+)

Preparation 2

To a 36 ml of 28% ammonia solution was added 17 g of isopropanesulfonyl chloride in 36 ml of acetone at 5°C, and then the mixture was stirred for 1 hour at room temperature. The reaction mixture was evaporated and the residue was extracted with a mixture of 200 ml of ethyl acetate and 200 ml of tetrahydrofuran. The organic layer was washed with brine and dried over magnesium sulfate. Concentration under reduced pressure gave 6.17 g of isopropanesulfonamide.

IR (KBr) : 3367, 3269, 1323, 1265, 1134 cm^{-1}

1H NMR (DMSO-d_6, δ) : 1.22 (d, J=6.8Hz, 6H), 3.00 (m, 1H), 6.65 (s, 2H)

APCI-MS (m/z) : 124 (MH^+)

mp : 47°C

Preparation 3

To a 15 ml of 28% ammonia solution was added 6.38 g of 1-octanesulfonyl chloride in 30 ml of acetone at 5°C, and then the mixture was stirred for 1 hour at 5°C. The reaction mixture was evaporated and 160 ml of water was added to the mixture. The mixture was adjusted to pH 3 with 1M

hydrochloric acid. The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 1-octanesulfonamide (3.96 g).

IR (KBr) : 3356, 3249, 1338, 1142 cm^{-1}

1H NMR (DMSO-d_6, δ) : 0.86 (m, 3H), 1.15-1.40 (m, 10H), 1.64 (m, 2H), 2.93 (m, 2H), 6.71 (broad s, 2H)

FAB-MS (m/z) : 194 (MH^+)

mp : 74°C

Preparation 4

To a stirred solution of phosphorous oxychloride was added 3-pyridinesulfonic acid and phosphorous pentachloride at room temperature and then the mixture was refluxed under nitrogen atmosphere for 8 hours. The reaction mixture was concentrated at atmospheric pressure. To the oily residue was added 300 ml of an ice-water and extracted with 600 ml of isopropyl ether. The organic layer was washed with brine, saturated $NaHCO_3$ and brine, and then dried over magnesium sulfate and evaporated. To a stirred solution of the residue in 30 ml of n-hexane was added 20 ml of 4M hydrochloric acid in ethyl acetate at 5°C and then the resulting precipitate was collected by filtration and washed with ethyl acetate to give 3-pyridinesulfonyl chloride hydrochloride (15.8 g).

IR(Nujol) : 2920, 1630, 1595, 1455, 1380 cm^{-1}

1H NMR (DMSO-d_6, δ) : 8.10 (dd, J=8.0, 5.8Hz, 1H), 8.73 (ddd, J=8.0, 1.8, 1.8Hz, 1H), 8.92 (d, J=5.8Hz, 1H), 8.99 (d, J=1.8Hz, 1H), 14.89 (broad s, 1H).

mp: 132-137°C

Preparation 5

To a 18 ml of 28% ammonia solution was added 10.6 g of 3-pyridinesulfonyl chloride hydrochloride in 18 ml of acetone at 5°C, and then the mixture was stirred for 2 hours at room temperature. The reaction mixture was evaporated and the

residue was extracted with a mixture of 200 ml of ethyl acetate and 200 ml of tetrahydrofuran. The organic layer was washed with brine and dried over magnesium sulfate. Concentration under reduced pressure gave a crystalline mass of 6.4 g of 3-pyridinesulfonamide.

IR(KBr) : 1576, 1468, 1417 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.63 (m, 3H), 8.19 (ddd, J=4.8, 2.3, 1.5Hz, 1H), 8.79 (dd, J=4.8, 1.5Hz, 1H), 8.98 (d, J=2.3Hz, 1H).

APCI-MS (m/z) : 159 (MH^+)

mp : 112°C

Preparation 6

A mixture of 4-nitro-1,2-phenylenediamine (3.06 g) and oxalic acid (3.60 g) in 4M hydrochloric acid (31 ml) was refluxed under nitrogen atmosphere for 4 hours and then cooled in an ice bath for 15 minutes. The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-nitro-2,3(1H,4H)-quinoxalinedione (4.20 g).

IR (KBr) : 1695 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.26 (d, J=9.2Hz, 1H), 7.96-8.01 (m, 2H), 12.16 (bs, 1H), 12.36 (bs, 1H)

APCI-MS (m/z) : 208 (MH^+)

mp : >300°C

Preparation 7

A mixture of 4-chloro-1,2-phenylenediamine (2.85 g) and oxalic acid (3.79 g) in 4M hydrochloric acid (43 ml) was refluxed under nitrogen atmosphere for 6 hours and then cooled in an ice bath for 30 minutes. The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-chloro-2,3(1H,4H)-quinoxalinedione (3.83 g).

IR(KBr) : 1693 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.12 (s, 3H), 11.99 (bs, 1H), 12.01 (bs, 1H)

APCI-MS (m/z) : 197(MH^+)

mp : >280°C

Preparation 8

A mixture of 4-fluoro-1,2-phenylenediamine (23.1 g) and oxalic acid (34.5 g) in 4M hydrochloric acid (230 ml) was refluxed under nitrogen atmosphere for 4 hours and then cooled in an ice bath for 20 minutes. The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-fluoro-2,3(1H,4H)-quinoxalinedione (34.49 g).

IR (KBr) : 1692 cm^{-1}

1H NMR (DMSO-d_6, δ) : 6.87-7.16 (m, 3H), 11.95 (bs, 1H), 11.99 (bs, 1H)

APCI-MS (m/z) : 181 (MH^+)

mp : >300°C

The following compounds (Preparations 9 and 10) were obtained according to the substantially similar manner to those of Preparations 6 to 8.

Preparation 9

6-Trifluoromethyl-2,3(1H,4H)-quinoxalinedione (21.41 g).

IR (KBr) : 1699 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.28 (d, J=8.2Hz, 1H), 7.40 (s, 1H), 7.44 (d, J=8.2Hz, 1H), 12.08 (bs, 1H), 12.19 (bs, 1H)

APCI-MS (m/z) : 231 (MH^+)

mp : >280°C

Preparation 10

6-Methoxy-2,3(1H,4H)-quinoxalinedione (18.64 g).

IR (KBr) : 1682 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.73 (s, 1H), 6.69 (d, J=2.7Hz, 1H), 6.71 (dd, J=9.0Hz, 2.7Hz, 1H), 7.05 (d, J=9.0Hz, 1H), 11.80 (bs, 1H), 11.85 (bs, 1H)

APCI-MS (m/z) : 193 (MH^+)

mp : >280°C

Preparation 11

To a suspension of 6-fluoro-2,3(1H,4H)-quinoxalinedione (5.30 g) in conc. sulfuric acid (53 ml) was added potassium nitrate (3.27 g) at 0-10°C. After stirred at room temperature under nitrogen atmosphere for 2 hours, the resulting solution was poured into ice-water (250 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-fluoro-7-nitro-2,3(1H,4H)-quinoxalinedione (5.97 g).

IR (KBr) : 1724, 1701 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.08 (d, J=12.0Hz, 1H), 7.86 (d, J=7.1Hz, 1H), 12.10 (bs, 1H), 12.37 (bs, 1H)

APCI-MS (m/z) : 226 (MH^+)

mp : >300°C

Preparation 12

To a suspension of 6-chloro-2,3(1H,4H)-quinoxalinedione (983 mg) in conc. sulfuric acid (10 ml) was added potassium nitrate (556 mg) at 0-5°C. After stirred at room temperature under nitrogen atmosphere for 2 hours, the resulting solution was poured into ice-water (50 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-chloro-7-nitro-2,3(1H,4H)-quinoxalinedione (1.20 g).

IR (KBr) : 1730, 1699 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.27 (s, 1H), 7.82 (s, 1H), 11.18 (bs, 1H), 12.30 (bs, 1H)

APCI-MS (m/z) : 242 (MH^+)

mp : >280°C

Preparation 13

To a suspension of 6-methoxy-2,3(1H,4H)-quinoxalinedione (1.92 g) in conc. sulfuric acid (19 ml) was added nitric acid (fuming, d=1.52)(1.03 ml) at 0-10°C. After stirred at room temperature under nitrogen atmosphere for 17 hours, the resulting solution was poured into ice-water (190 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo. The precipitate was dissolved in N,N-dimethylformamide (30 ml) at 120°C, and the solution was filtered. A mixture of the filtrate and water (90 ml) was stirred in an ice bath, and the resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-methoxy-7-nitro-2,3(1H,4H)-quinoxalinedione (990 mg).

IR (KBr) : 1693 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.88 (s, 3H), 6.91 (s, 1H), 7.73 (s, 1H), 11.95 (bs, 1H), 12.17 (bs, 1H)

APCI-MS (m/z) : 238 (MH^+)

mp : >280°C

Preparation 14

To a suspension of 2(1H)-quinoxalinone (14.62 g) in conc. sulfuric acid (146 ml) was added potassium nitrate (12.13 g) at 0-5°C under nitrogen atmosphere. After stirred at room temperature for 2 hours, the resulting solution was poured into ice-water (700 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-nitro-2(1H)-quinoxalinone (17.20 g).

IR (KBr) : 1670, 1616, 1529, 1344 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.44 (d, J=9.0Hz, 1H), 8.32 (s, 1H), 8.37 (dd, J=9.0Hz, 2.5Hz, 1H), 8.52 (d, J=2.5Hz, 1H), 12.91 (bs, 1H), 12.37 (bs, 1H)

APCI-MS (m/z) : 192 (MH^+)

mp : >280°C

Preparation 15

A mixture of 6-nitro-2,3(1H,4H)-quinoxalinedione (4.14 g) and phosphorous oxychloride (9.32 ml) was refluxed under nitrogen atmosphere for 24 hours. After cooled in an ice bath, the reaction mixture was poured into a mixture of ice-water (100 ml) and dichloromethane (100 ml) and stirred for 30 minutes. The resulting precipitate was removed by filtration, and the separated organic layer was washed with aqueous sodium hydrogen carbonate and brine, and dried over magnesium sulfate, and evaporated. The residue was suspended in isopropyl ether (60 ml), and the resulting precipitate was collected by filtration and washed with isopropyl ether and dried in vacuo to give 2,3-dichloro-6-nitroquinoxaline (3.68 g).

IR (KBr) : 1527 cm^{-1}

1H NMR (DMSO-d_6, δ) : 8.33 (d, J=9.1Hz, 1H), 8.62 (dd, J=9.1Hz, 2.4Hz, 1H), 8.92 (d, J=2.4Hz, 1H)

mp : 152°C

Preparation 16

To a suspension of 6-chloro-7-nitro-2,3(1H,4H)-quinoxalinedione (12.08 g) in phosphorous oxychloride (120 ml) was added N,N-dimethylformamide (1 ml), and the mixture was refluxed under nitrogen atmosphere for one hour. After cooled in an ice bath, the reaction mixture was poured into ice-water (800 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 2,3,6-trichloro-7-nitroquinoxaline (12.98 g).

IR (KBr) : 1602, 1535, 1257, 1153, 1008 cm^{-1}

1H NMR (DMSO-d_6, δ) : 8.62 (s, 1H), 8.92 (s, 1H)

mp : 140°C

Preparation 17

To a suspension of 6-fluoro-7-nitro-2,3(1H,4H)-quinoxalinedione (4.50 g) in phosphorous oxychloride (45 ml)

was added N,N-dimethylformamide (0.5 ml), and the mixture was refluxed under nitrogen atmosphere for 90 minutes. After cooled in an ice bath, the reaction mixture was poured into ice-water (350 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 2,3-dichloro-6-fluoro-7-nitroquinoxaline (4.58 g).

IR(KBr) : 1626, 1570, 1543, 1338, 1207, 1011 cm^{-1}

1H NMR (DMSO-d_6, δ) : 8.38 (d, J=11.5Hz, 1H), 8.95 (d, J=7.6Hz, 1H)

mp : 135-136 °C

The following compounds (Preparations 18 and 19) were obtained according to the substantially similar manner to those of Preparations 16 and 17.

Preparation 18

2,3-Dichloro-6-trifluoromethylquinoxaline (2.55 g).

IR(KBr) : 1319, 1277, 1180, 1126, 999 cm^{-1}

1H NMR (DMSO-d_6, δ) : 8.21 (dd, J=8.8Hz, 1.9Hz, 1H), 8.31 (d, J=8.8Hz, 1H), 8.53 (d, J=1.9Hz, 1H)

mp : 82°C

Preparation 19

2,3-Dichloro-6-methoxy-7-nitroquinoxaline (642 mg).

IR (KBr) : 1622, 1531, 1269, 1223, 1136, 1011 cm^{-1}

1H NMR (DMSO-d_6, δ) : 4.09 (s, 1H), 7.88 (s, 1H), 8.70 (s, 1H)

APCI-MS (m/z) : 274 (M^+)

mp : 183-185°C

Preparation 20

A mixture of 6-nitro-2(1H)-quinoxalinone (47.8 g) and phosphorous oxychloride (183 ml) was refluxed under nitrogen atmosphere for 3 hours. After cooled in an ice bath, the reaction mixture was poured into ice-water (1800 ml). The

resulting precipitate was collected by filtration and washed with water and triturated with ethyl acetate (150 ml). The resulting precipitate was collected by filtration and washed with ethyl acetate and dried in vacuo to give 2-chloro-6-nitroquinoxaline (43.0 g).

IR (KBr) : 1674, 1527, 1346 cm^{-1}

1H NMR (DMSO-d_6, δ) : 8.30 (d, J=9.2Hz, 1H), 8.63 (dd, J=9.2Hz, 2.5Hz, 1H), 8.97 (d, J=2.5Hz, 1H), 9.22 (s, 1H)

FAB-MS (m/z) : 209 (M^+)

mp : 199-202°C (decomp.)

Preparation 21

A mixture of 2(1H)-quinoxalinone (25.0 g) and phosphorous oxychloride (118 ml) was refluxed under nitrogen atmosphere for 90 minutes. After cooled in an ice bath, the reaction mixture was poured into ice-water (1300 ml). The resulting precipitate was collected by filtration and washed with water and air-dried at room temperature to give 2-chloroquinoxaline (20.88 g).

IR (KBr) : 1541, 1487, 1093, 958, 760 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.88-8.21 (m, 4H), 9.01 (s, 1H)

APCI-MS (m/z) : 165(MH^+)

mp : 46°C

Preparation 22

To a suspension of sodium hydride (60% oil dispersion, 2.61 g) in N,N-dimethylformamide (80 ml) was added methanesulfonamide (3.16 g) at 0-5°C under nitrogen atmosphere, and the mixture was stirred at room temperature for 15 minutes. 2,3-Dichloro-6-nitroquinoxaline (7.96 g) was added to the mixture at 0-5°C, and the resulting solution was stirred at room temperature for one hour and then poured into a mixture of cold water (400 ml) and ethyl acetate (400 ml). To the separated aqueous layer was added ethyl acetate (400

ml), and the mixture was adjusted to pH 2 with 6M hydrochloric acid. The organic layer was washed with brine and dried over magnesium sulfate and evaporated. A suspension of the residue in ethanol (120 ml) was refluxed for 15 minutes and cooled in an ice bath. The resulting precipitate was collected by filtration and washed with ethanol and dried in vacuo to give 3-chloro-2-methylsulfonylamino-6-nitroquinoxaline (8.60 g).

IR (KBr) : 1560, 1535, 1459, 1168 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.45 (s, 3H), 8.09 (d, J=9.2Hz, 1H), 8.48 (dd, J=9.2Hz, 2.5Hz, 1H), 8.70 (d, J=2.5Hz, 1H)

FAB-MS (m/z) : 303 (M^+)

mp : 191-192°C

Preparation 23

To a suspension of sodium hydride (60% oil dispersion, 400 mg) in N,N-dimethylformamide (14 ml) was added methanesulfonamide (476 mg) at 0-5°C under nitrogen atmosphere, and the mixture was stirred at room temperature for 30 minutes. 2,3,6-Trichloro-7-nitroquinoxaline (1.39 g) was added to the mixture at 0-5°C, and the resulting solution was stirred at 0-5°C for one hour and then poured into a mixture of cold water (100 ml) and ethyl acetate (100 ml). After adjusted to pH 2 with 6M hydrochloric acid, the separated organic layer was washed with brine and dried over magnesium sulfate and evaporated. A suspension of the residue in ethanol (20 ml) was refluxed for 30 minutes and then cooled in an ice bath. The resulting precipitate was collected by filtration and washed with ethanol and dried in vacuo to give 2,6-dichloro-3-methylsulfonylamino-7-nitroquinoxaline (1.53 g).

IR(KBr) : 1560, 1538, 1454, 1168 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.46 (s, 3H), 8.30 (s, 1H), 8.67 (s, 1H)

FAB-MS (m/z) : 337 (M^+)
mp : 245°C (decomp.)

Preparation 24

To a suspension of sodium hydride (60% oil dispersion, 800 mg) in N,N-dimethylformamide (26 ml) was added methanesulfonamide (951 mg) at 0-5°C under nitrogen atmosphere, and the mixture was stirred at room temperature for one hour. 2,3-Dichloro-6-fluoro-7-nitroquinoxaline (2.62 g) was added to the mixture at 0-5°C, and the resulting solution was stirred at room temperature for one hour and then poured into a mixture of cold water (130 ml) and ethyl acetate (130 ml). After adjusted to pH 2 with 6M hydrochloric acid, the resulting precipitate was collected by filtration, and washed with water and ethyl acetate, and dried in vacuo to give 2-chloro-6-fluoro-3-methylsulfonylamino-7-nitroquinoxaline (2.14 g).

IR (KBr) : 1545, 1462, 1171, 858 cm^{-1}
1H NMR (DMSO-d_6, δ) : 3.43 (s, 3H), 8.01 (d, J=12.4Hz, 1H), 8.68 (d, J=7.8Hz, 1H)
FAB-MS (m/z) : 321 (M^+)
mp : 252-253°C

The following compounds (Preparations 25 to 27) were obtained according to substantially the similar manner to those of Preparations 22 to 24.

Preparation 25

3-Chloro-2-methylsulfonylamino-6-trifluoromethylquinoxaline (1.46 g).

IR (KBr) : 1464, 1159, 1126 cm^{-1}
1H NMR (DMSO-d_6, δ) : 3.49 (s, 3H), 8.05 (dd, J=8.8Hz, 1.9Hz, 1H), 8.15 (d, J=8.8Hz, 1H), 8.32 (d, J=1.9Hz, 1H)
FAB-MS (m/z) : 326 (M^+)

mp : 216°C

Preparation 26

2-Chloro-3-methylsulfonylamino-6-methoxy-7-nitroquinoxaline (260 mg).

IR (KBr) : 1561, 1527, 1464, 1153 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.49 (s, 3H), 4.06 (s, 3H), 7.69 (s, 1H), 8.48 (s, 1H)

APCI-MS (m/z) : 333 (MH^+)

mp : 275°C (decomp.)

Preparation 27

2-Methylsulfonylamino-6-nitroquinoxaline (12.43 g).

IR (KBr) : 1673 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.43 (s, 3H), 7.79 (d, J=9.6Hz, 1H), 8.03-8.07 (m, 3H), 11.23 (bs, 1H), 12.85 (bs, 1H)

APCI-MS (m/z) : 285 (MH^+)

mp : 251°C

Preparation 28

To a suspension of sodium hydride (60% oil dispersion, 400 mg) in N,N-dimethylformamide (15 ml) was added isopropanesulfonamide (616 mg) at 0-5°C under nitrogen atmosphere, and the mixture was stirred at room temperature for 15 minutes. 2,3-Dichloro-6-nitroquinoxaline (1.22 g) was added to the mixture at 0-5°C, and the resulting solution was stirred for 2 hours with warming up to room temperature and then poured into a mixture of cold water (250 ml) and ethyl acetate (250 ml). The mixture was adjusted to pH 2 with 6M hydrochloric acid. The organic layer was washed with brine and dried over magnesium sulfate and evaporated.
A suspension of the residue in ethanol (40 ml) was refluxed for 15 minutes and cooled in an ice bath. The resulting precipitate was collected by filtration and washed with

ethanol and dried in vacuo to give 3-chloro-2-isopropylsulfonylamino-6-nitroquinoxaline (1.16 g).

IR (KBr) : 3236, 1533, 1460, 1429, 1346, 1170 cm^{-1}

1H NMR (DMSO-d_6, δ) : 1.39 (d, J=6.8Hz, 6H), 3.97 (m, 1H), 8.11 (d, J=9.1Hz, 1H), 8.47 (dd, J=9.1, 2.5Hz, 1H), 8.68 (d, J=2.5Hz, 1H).

FAB-MS (m/z) : 331 (M^+), 133, 119.

mp : 196°C

Preparation 29

To a suspension of sodium hydride (60% oil dispersion, 240 mg) in N,N-dimethylformamide (15 ml) was added octanesulfonamide (580 mg) at 0-5°C under nitrogen atmosphere, and the mixture was stirred at room temperature for 15 minutes. 2,3-Dichloro-6-nitroquinoxaline (732 mg) was added to the mixture at 0-5°C, and the resulting solution was stirred at room temperature for 2 hours and then poured into a mixture of cold water (200 ml) and ethyl acetate (200 ml). The mixture was adjusted to pH 2 with 6M hydrochloric acid. The organic layer was washed with brine and dried over magnesium sulfate and evaporated. The residue was suspended in isopropyl ether (40 ml) and the resulting precipitate was collected by filtration and washed with a mixture of n-hexane and isopropyl ether (1:1) and dried in vacuo to give 3-chloro-2-octylsulfonylamino-6-nitroquinoxaline (951 mg).

IR (KBr) : 3248, 1531, 1464, 1344, 1162 cm^{-1}

1H NMR (DMSO-d_6, δ) : 0.81 (m, 3H), 1.05-1.50 (m, 10H), 1.77 (m, 2H), 3.65 (m, 2H), 8.11 (d, J=9.2Hz, 1H), 8.49 (dd, J=9.2, 2.6Hz, 1H), 8.71 (d, J=2.6Hz, 1H).

FAB-MS (m/z) : 401 (M^+), 225, 133

mp : 119°C

Preparation 30

To a suspension of sodium hydride (60% oil dispersion, 7.68 g) in N,N-dimethylformamide (66 ml) was added

methanesulfonamide (9.14 g) at 0-10°C under nitrogen atmosphere, and the mixture was stirred at 0-10°C for 10 minutes. 2-Chloroquinoxaline (6.58 g) was added to the mixture at 0-10°C, and the resulting solution was stirred at 80°C for 4 hours and then poured into a mixture of cold water (350 ml) and ethyl acetate (350 ml). The insoluble material was removed by filtration, and a mixture of the separated aqueous layer and ethyl acetate (700 ml) was adjusted to pH 1.5 with 6M hydrochloric acid, and the organic layer was washed with brine and dried over magnesium sulfate and evaporated. The residue was triturated with isopropyl ether (60 ml), and the resulting precipitate was collected by filtration and washed with isopropyl ether and dried in vacuo to give 2-methylsulfonylaminoquinoxaline (3.34 mg).

IR (KBr) : 1583, 1506, 1468, 1325, 1163, 895, 764, 509 cm-1

1H NMR (DMSO-d_6, δ) : 3.46 (s, 3H), 7.56-8.02 (m, 4H), 8.61 (s, 1H), 11.52 (bs, 1H)

FAB-MS (m/z) : 224 (MH^+)

mp : 159°C

Preparation 31

To a suspension of sodium hydride (60% oil dispersion, 0.96 g) in N,N-dimethylformamide (21 ml) was added benzenesulfonamide (1.89 g) at 0-10°C under nitrogen atmosphere, and the mixture was stirred at 0-10°C for 15 minutes. 2-Chloro-6-nitroquinoxaline (2.10 g) was added to the mixture at 0-10°C, and the resulting solution was stirred at room temperature for one hour and then poured into a mixture of cold water (100 ml) and ethyl acetate (100 ml). A mixture of the separated aqueous layer, ethyl acetate (100 ml) and tetrahydrofuran (50 ml) was adjusted to pH 1.5 with 6M hydrochloric acid, and the organic layer was washed with brine and dried over magnesium sulfate and evaporated. Recrystallization of the residue from a mixture of ethanol

and tetrahydrofuran gave 2-phenylsulfonylamino-6-nitroquinoxaline (1.84 g).

IR (KBr): 1546, 1531, 1348, 1160 cm^{-1}

1H NMR (DMSO-d_6, δ): 7.75-7.72 (m, 3H), 7.94 (d, J=9.1Hz, 1H), 8.13-8.18 (m, 2H), 8.45 (dd, J=9.1Hz, 2.6Hz, 1H), 8.71 (d, J=2.6Hz, 1H), 8.76 (s, 1H)

APCI-MS (m/z): 331(MH^+)

mp: 223-225°C (decomp.)

Preparation 32

To a suspension of sodium hydride (60% oil dispersion, 160 mg) in N,N-dimethylformamide (10 ml) was added 3-pyridinesulfonamide (316 mg) at 0-5°C under nitrogen atmosphere, and the mixture was stirred at room temperature for 15 minutes. 2,3-Dichloro-6-nitroquinoxaline (488 mg) was added to the mixture at 0-5°C, and the resulting solution was stirred at 5°C for 1 hour and then poured into a mixture of cold water (200 ml) and ethyl acetate (200 ml). The separated aqueous layer was adjusted to pH 4 with 6M hydrochloric acid. The resulting precipitate was collected by filtration and washed with water. A suspension of the precipitate in ethanol (20 ml) was refluxed for 15 minutes and cooled in an ice bath. The resulting precipitate was collected by filtration and washed with ethanol and dried in vacuo to give 3-chloro-2-[(3-pyridyl)sulfonylamino]-6-nitroquinoxaline (427 mg).

IR (KBr): 1618, 1535, 1514, 1416, 1338 cm^{-1}

1H NMR (DMSO-d_6, δ): 7.72-7.83 (m, 2H), 8.32 (m, 1H), 8.50 (m, 1H), 8.74 (m, 2H), 9.34 (s, 1H)

APCI-MS (m/z): 366 (MH^+)

mp: 274°C

Preparation 33

To a suspension of sodium hydride (60% oil dispersion, 880 mg) in N,N-dimethylformamide (36 ml) was added

sulfamide (1.06 g) at 0-10°C under nitrogen atmosphere, and the mixture was stirred at room temperature for one hour. 2,3-Dichloro-6-nitroquinoxaline (2.44 g) was added to the mixture at 0-10°C, and the resulting solution was stirred at room temperature for one hour and then poured into a mixture of cold water (250 ml) and ethyl acetate (250 ml). To the separated aqueous layer was added ethyl acetate (250 ml), and the mixture was adjusted to pH 1.5 with 6M hydrochloric acid. The organic layer was washed with brine and dried over magnesium sulfate and evaporated. A suspension of the residue in ethanol (34 ml) was refluxed for 30 minutes and then cooled in an ice bath. The resulting precipitate was collected by filtration and washed with ethanol and dried in vacuo to give 3-chloro-6-nitro-2-sulfamidoquinoxaline (1.88g).

IR (KBr): 1560, 1531, 1466, 1429, 1342, 1279, 1167 cm^{-1}

1H NMR (DMSO-d_6, δ): 8.22 (d, J=9.2Hz, 1H), 8.53 (dd, J=9.2Hz, 2.5Hz, 1H), 8.70 (d, J=2.5Hz, 1H)

FAB-MS (m/z): 303.9 (M^+)

mp: 205-206°C (decomp.)

Preparation 34

To a suspension of sodium hydride (60% oil dispersion, 240 mg) in N,N-dimethylformamide (7.3 ml) was added N-methylmethanesulfonamide (327 mg) at 0-5°C under nitrogen atmosphere, and the mixture was stirred at room temperature for 30 minutes. 2,3-Dichloro-6-nitroquinoxaline (732 mg) was added to the mixture at 0-5°C, and the resulting solution was stirred at room temperature for 2 hours and then poured into a mixture of cold water (80 ml) and ethyl acetate (80 ml). To the separated aqueous layer was added ethyl acetate (80 ml), and the mixture was adjusted to pH 4 with 1M hydrochloric acid. The organic layer was washed with brine and dried over magnesium sulfate and evaporated. 2-[(N-Methyl)-methylsulfonylamino]-3-chloro-6-nitroquinoxaline (160 mg) was

obtained from the residue by column chromatography on silica gel (15 g).

IR (KBr): 1531, 1344, 1153 cm^{-1}

1H NMR (DMSO-d_6, δ): 3.39 (s, 3H), 3.51 (s, 3H), 8.36 (d, J=9.2Hz, 1H), 8.62(dd, J=9.2Hz, 2.5Hz, 1H), 8.91 (d, J=2.5Hz, 1H)

FAB-MS (m/z): 317 (M^+)

mp: 173-175°C

Preparation 35

Keeping below 30°C with ice cooling, 2(1H)-quinoxalinone (14.62 g) was added to chlorosulfonic acid (73 ml), and the reaction mixture was stirred at 120°C under nitrogen atmosphere for 20 hours. After cooled in an ice bath, the mixture was poured into ice-water (600 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-chlorosulfonyl-2(1H)-quinoxalinone (19.25 g).

IR (KBr): 1678, 1599, 1371, 1192, 1165, 646, 604, 501 cm^{-1}

1H NMR (DMSO-d_6, δ): 7.28 (d, J=8.4Hz, 1H), 7.78 (dd, J=8.4Hz, 1.8Hz, 1H), 7.94 (d, J=1.8Hz, 1H), 8.19 (s, 1H), 14.40 (bs, 1H)

FAB-MS (m/z): 245 (MH^+)

mp: 198-199°C (decomp.)

Preparation 36

To a suspension of 6-chlorosulfonyl-2(1H)-quinoxalinone (8.56 g) in water (86 ml) was added dropwise 50% aqueous dimethylamine (11.04 ml) at room temperature. After stirred at 60°C under nitrogen atmosphere for 2 hours, the reaction mixture was cooled in an ice bath. The mixture was adjusted to pH 7 with 1M hydrochloric acid, and the resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-(dimethylamino)sulfonyl-2(1H)-

quinoxalinone (8.50 g).

IR (KBr) : 1680, 1338, 1138, 957, 710, 503 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.64 (s, 6H), 7.50 (d, J=8.6Hz, 1H), 7.87 (dd, J=8.6Hz, 2.1Hz, 1H), 8.06 (d, J=2.1Hz, 1H), 8.30 (s, 1H), 12.80 (bs, 1H)

FAB-MS (m/z) : 254 (MH^+)

mp : 271°C

Preparation 37

A mixture of 6-(dimethylamino)sulfonyl-2(1H)-quinoxalinone (2.53 g) and phosphorous oxychloride (20 ml) was refluxed under nitrogen atmosphere for 2 hours. After cooled in an ice bath, the reaction mixture was poured into ice-water (100 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 2-chloro-6-(dimethylamino)sulfonylquinoxaline (2.43 g).

IR (KBr) : 1547, 1342, 1144, 1088, 947, 727, 577 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.72 (s, 6H), 8.18 (dd, J=8.8Hz, 2.0Hz, 1H), 8.30 (d, J=8.8Hz, 1H), 8.47 (d, J=2.0Hz, 1H), 9.19 (s, 1H)

APCI-MS (m/z) : 272 (MH^+)

mp : 272-273°C (decomp.)

Preparation 38

To a suspension of sodium hydride (60% oil dispersion, 768 g) in N,N-dimethylformamide (22 ml) was added methanesulfonamide (913 mg) at 0-5°C under nitrogen atmosphere, and the mixture was stirred at 0-5°C for 10 minutes. 2-Chloro-6-(dimethylamino)sulfonylquinoxaline (2.17 g) was added to the mixture at 0-5°C, and the resulting solution was stirred at room temperature for 3 hours and then poured into a mixture of cold water (100 ml) and ethyl acetate (100 ml). The separated aqueous layer was washed with ethyl acetate and adjusted to pH 2 with 6M hydrochloric acid and stirred in an ice bath for 30 minutes. The resulting

precipitate was collected by filtration and washed with water and dried in vacuo to give 6-(dimethylamino)sulfonyl-2-methylsulfonylaminoquinoxaline (2.28 g).

IR (KBr): 1579, 1471, 1335, 1142, 958, 874, 721, 571 cm^{-1}

1H NMR (DMSO-d_6, δ): 2.68 (s, 6H), 2.50 (s, 3H), 7.99-8.10 (m, 2H), 8.28 (s, 1H), 8.70 (s, 1H), 11.91 (bs, 1H)

APCI-MS (m/z): 331 (MH^+)

mp: 232°C

Preparation 39

To a suspension of sodium hydride (60% oil dispersion, 400 mg) in N,N-dimethylformamide (15 ml) was added 3-chloro-2-methylsulfonylamino-6-nitroquinoxaline (1.51 mg) at 0-5°C under nitrogen atmosphere, and the mixture was stirred at room temperature for 30 minutes. Methyl iodide (0.77 ml) was added to the mixture at 0-5°C, and the reaction mixture was stirred at 50°C for 18 hours and then poured into a mixture of cold water (100 ml) and ethyl acetate (100 ml). The organic layer was washed with aqueous sodium hydrogen carbonate and brine, and was dried over magnesium sulfate and evaporated. 2-[(N-Methyl)methylsulfonylamino]-3-chloro-6-nitroquinoxaline (150 mg) was obtained from the residue by column chromatography on silica gel (24 g).

IR (KBr): 1531, 1344, 1153 cm^{-1}

1H NMR (DMSO-d_6, δ): 3.39 (s, 3H), 3.51 (s, 3H), 8.35 (d, J=9.2Hz, 1H), 8.62 (dd, J=9.2Hz, 2.5Hz, 1H), 8.91 (d, J=2.5Hz, 1H)

FAB-MS (m/z): 317 (M^+)

mp: 173-175°C

Preparation 40

To a 21 ml of 28% ammonia solution was added 9 g of ethanesulfonyl chloride in 21 ml of acetone at 5°C, and then

the mixture was stirred for 2 hours at room temperature. The reaction mixture was evaporated and the residue was extracted with a mixture of 150 ml of ethyl acetate and 150 ml of tetrahydrofuran. The organic layer was washed with brine and dried over magnesium sulfate. Concentration under reduced pressure gave 5.4 g of ethanesulfonamide as a brown oil.

1H NMR (DMSO-d_6, δ) : 6.72 (m, 2H), 2.51 (q, J=7.4Hz, 2H), 1.22 (t, J=7.4Hz, 3H)

APCI-MS (m/z) : 110 (MH^+)

The following compounds (Preparations 41 and 42) were obtained according to a similar manner to that of Preparation 40.

Preparation 41

Propanesulfonamide

IR (KBr) : 3348, 3259, 1317, 1290, 1140 cm^{-1}

1H NMR (DMSO-d_6, δ) : 0.97 (t, J=7.4Hz, 3H), 1.70 (m, 2H), 2.93 (m, 2H), 6.71 (broad s, 2H)

APCI-MS (m/z) : 124 (MH^+)

mp : 52℃

Preparation 42

Butanesulfonamide

IR (KBr) : 3344, 3255, 1321, 1302, 1273, 1142 cm^{-1}

1H NMR (DMSO-d_6, δ) : 0.89 (t, J=7.2Hz, 3H), 1.26-1.48 (m, 2H), 1.58-1.73 (m, 2H), 2.95 (m, 2H), 6.73 (s, 2H)

APCI-MS (m/z) : 138 (MH^-)

mp : 45℃

Preparation 43

To a stirred mixture of 2-nitro-4-trifluoromethoxyaniline (4.44 g) and 3.9 ml of triethylamine in 40 ml of DMF was added 2.9 ml of ethyl chloroglyoxylate in

10 ml of DMF at 0~10℃. After stirred at 5°C under nitrogen atmosphere for 1 hour, the resulting solution was poured into ice-water (300 ml). The resulting residue was collected by filtration and washed with water. A solution of the residue in 200 ml of acetone was added to a stirred mixture of 108 g of titanium(III)chloride solution and 50 ml of water at 0~10℃. After stirred at room temperature for 3 hours, the resulting solution was extracted with ethyl acetate. The organic layer was washed with brine and dried over MgSO4 and evaporated. The resulting residue was triturated in isopropyl ether. The resulting precipitate was collected by filtration and washed with isopropyl ether and dried in vacuo to give 6-trifluoromethoxy-2,3(1H,4H)-quinoxalinedione (2.43 g).

IR (KBr): 1716, 1702, 1628, 1394, 1257 cm^{-1}

1H NMR (DMSO-d_6, δ): 7.07-7.12 (m, 2H), 7.20 (dd, J=7.0, 2.5Hz, 1H), 12.00 (broad s, 2H)

FAB-MS (m/z): 247 (MH^+)

mp: >280℃

Preparation 44

To a stirred mixture of 4-amino-3-nitrobenzonitrile (4.89 g) and 5.0 ml of triethylamine in 100 ml of DMF was added 4.5 g of ethyl chloroglyoxylate in 20 ml of DMF at 0~10℃. After stirred at room temperature under nitrogen atmosphere for 2 hours, the resulting solution was poured into ice-water (800 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 4-ethoxalylamino-3-nitrobenzonitrile (7.43 g).

IR (KBr): 1724, 1622, 1579, 1522, 1448 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.34 (t, J=7.1Hz, 3H), 4.36 (q, J=7.1Hz, 2H), 8.24 (dd, J=8.6, 1.6Hz, 1H), 8.33 (d, J=8.6Hz, 1H), 8.69 (d, J=1.6Hz, 1H)

FAB-MS (m/z): 263 (M^+)

mp: 151℃

Preparation 45

To a stirred mixture of 270 g of titanium(III)chloride solution and 130 ml of water was added 13.2 g of 4-ethoxalylamino-3-nitrobenzonitrile in 390 ml of acetone at 0~10℃. After stirred at room temperature for 3 hours, the resulting solution was poured into ice-water (3000 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-cyano-2,3(1H,4H)-quinoxalinedione (8.77 g).

IR (KBr) : 1761, 1728, 1672, 1612, 1495 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.22 (d, J=8.3Hz, 1H), 7.41 (d, J=1.7Hz, 1H), 7.51 (dd, J=8.3, 1.8Hz, 1H), 12.09 (s, 1H), 12.22 (s, 1H).

FAB-MS (m/z) : 187 (M^+)

mp : >280℃

Preparation 46

A mixture of 4-methyl-1,2-phenylenediamine (25.54 g) and oxalic acid (39.63 g) in 4M hydrochloric acid (255 ml) was refluxed under nitrogen atmosphere for 4 hours and then cooled in an ice bath for 30 minutes. The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-methyl-2,3(1H,4H)-quinoxalinedione (38.7 g).

IR (KBr) : 1695, 1394 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.27 (s, 3H), 6.90 (d, J=8.2Hz, 1H), 6.92 (s, 1H), 7.02 (d, J=8.2Hz, 1H), 11.85 (bs, 2H), 12.36 (bs, 1H)

APCI-MS (m/z) : 177 (MH^+)

mp : >280℃

The following compounds (Preparations 47 and 48) were obtained according to a similar manner to that of Preparation 11.

Preparation 47

6-Methyl-7-nitro-2,3(1H,4H)-quinoxalinedione (6.16 g).
IR (KBr): 1700, 1539, 1400, 1323 cm^{-1}
1H NMR (DMSO-d_6, δ): 2.51 (s, 3H), 7.05 (s, 1H), 7.82 (s, 1H), 12.05 (bs, 1H), 12.24 (bs, 1H)
APCI-MS (m/z): 222 (MH^+)
mp: >280℃

Preparation 48

6-Nitro-7-trifluoromethoxy-2,3(1H,4H)-quinoxalinedione (821 mg).
IR (KBr): 1728, 1703, 1618, 1547 cm^{-1}
1H NMR (DMSO-d_6, δ): 7.25 (s, 1H), 7.89 (s, 1H), 12.26 (broad s, 2H)
FAB-MS (m/z): 292 (MH^+)
mp: >280℃

The following compound (Preparation 49) was obtained according to a similar manner to that of Preparations 16 and 17.

Preparation 49

2,3-Dichloro-6-nitro-7-trifluoromethoxyquinoxaline
IR (KBr): 1622, 1539, 1485, 1352 cm^{-1}
1H NMR (DMSO-d_6, δ): 8.51 (s, 1H), 9.01 (s, 1H)
FAB-MS (m/z): 329 (MH^+)
mp: 97℃

Preparation 50

To a suspension of 6-methyl-7-nitro-2,3(1H,4H)-quinoxalinedione (5.97 g) in phosphorous oxychloride (60 ml) was added N,N-dimethylformamide (2.5 ml), and the mixture was refluxed under nitrogen atmosphere for 2 hours. After cooled in an ice bath, the reaction mixture was poured into ice-water (600 ml). After adjustment to pH 5 with aqueous sodium

hydroxide solution, the resulting precipitate was collected by filtration and washed with water. The solution of the precipitate in ethyl acetate (200 ml) was washed with aqueous sodium hydrogen carbonate (200 ml) and brine(200 ml), dried over magnesium sulfate. Column chromatography of the residue on silica gel gave 2,3-dichloro-6-methyl-7-nitroquinoxaline (4.97 g).

IR (KBr) : 1533, 1363, 1261, 1188, 1128, 1001 cm^{-1}

1H NMR ($CDCl_3$, δ) : 2.77(s, 3H), 7.99 (s, 1H), 8.58 (s, 1H)

mp : 139 ℃

Preparation 51

To a stirred solution of phosphorous oxychloride (7 ml) was added 187 mg of 6-cyano-2,3(1H,4H)-quinoxalinedione, 417 mg of phosphorous pentachloride and 0.5 ml of DMF at room temperature, and then the mixture was refluxed under nitrogen atmosphere for 24 hours. After cooled at room temperature, the resulting solution was poured into ice-water (300 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 2,3-dichloro-6-cyanoquinoxaline (162 mg).

IR (KBr) : 2231, 1545, 1485, 1257 cm^{-1}

1H NMR (DMSO-d_6, δ) : 8.26 (m, 2H), 8.77 (m, 1H)

mp : 244℃

The following compounds (Preparations 52 to 62) were obtained according to substantially the similar manners to those of Preparations 22 to 24.

Preparation 52

2-Chloro-3-methylsulfonylamino-7-nitro-6-trifluoromethoxyquinoxaline

IR (KBr) : 1624, 1568, 1541, 1458, 1350 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.44 (s, 3H), 8.16 (s, 1H), 8.73

(s, 1H)
FAB-MS (m/z) : 387 (MH^+)
mp : 209℃

Preparation 53
3-Chloro-6-cyano-2-methylsulfonylaminoquinoxaline
IR (KBr) : 1610, 1562, 1454, 1425, 1344 cm^{-1}
1H NMR (DMSO-d_6, δ) : 3.49 (s, 3H), 8.08 (m, 2H), 8.52 (s, 1H)
FAB-MS (m/z) : 283 (MH^+)
mp : 250℃ (decomp.)

Preparation 54
2-Chloro-3-methylsulfonylamino-6-methyl-7-nitroquinoxaline
IR (KBr) : 1562, 1533, 1450, 1360, 1336, 1165, 1078, 972, 858 cm^{-1}
1H NMR (DMSO-d_6, δ) : 2.66 (s, 3H), 3.45 (s, 3H), 8.00 (s, 1H), 8.53 (s, 1H)
APCI-MS (m/z) : 317 (MH^+)
mp : 239℃

Preparation 55
3-Chloro-2-ethylsulfonylamino-6-nitroquinoxaline
IR (KBr) : 3232, 1531, 1458, 1427, 1348, 1161 cm^{-1}
1H NMR (DMSO-d_6, δ) : 1.33 (t, J=7.4Hz, 3H), 3.66 (q, J=7.4Hz, 2H), 8.10 (d, J=9.2Hz, 1H), 8.48 (dd, J=9.2, 2.5Hz, 1H), 8.70 (d, J=2.5Hz, 1H)
FAB-MS (m/z) : 317(M^+)
mp : 218℃

Preparation 56
2-Chloro-6-fluoro-3-ethylsulfonylamino-7-nitroquinoxaline
IR (KBr) : 1626, 1564, 1537, 1458, 1431, 1342, 1161,

1072, 852 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.31 (t, J=7.3Hz, 3H), 3.64 (q, J=7.3Hz, 2H), 8.03 (d, J=12.3Hz, 1H), 8.68 (d, J=7.8Hz, 1H)

mp: 247~248℃

Preparation 57

3-Chloro-6-nitro-2-propylsulfonylaminoquinoxaline

IR (KBr): 3234, 1562, 1531, 1456, 1425, 1346, 1161 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.02 (m, 3H), 1.82 (m, 2H), 3.62 (m, 2H), 8.11 (d, J=9.2Hz, 1H), 8.48 (dd, J=9.2, 2.5Hz, 1H), 8.70 (d, J=2.5Hz, 1H).

FAB-MS (m/z): 331 (M^+)

mp: 207℃

Preparation 58

2-Chloro-6-fluoro-3-propylsulfonylamino-7-nitroquinoxaline

IR (KBr): 1626, 1564, 1537, 1456, 1433, 1340, 1161, 1070, 854 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.02 (t, J=7.4Hz, 3H), 1.71~1.90 (m, 2H), 3.57~3.65 (m, 2H), 8.04 (d, J=12.3Hz, 1H), 8.68 (d, J=7.7Hz, 1H)

FAB-MS (m/z): 348 (M^+)

mp: 235~236℃

Preparation 59

2-Chloro-6-fluoro-3-isopropylsulfonylamino-7-nitroquinoxaline

IR (KBr): 1632, 1560, 1460, 1342, 1146, 1070, 849 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.37 (d, J=6.8Hz, 6H), 4.01 (sep, J=6.8Hz, 1H), 8.02 (d, J=12.3Hz, 1H), 8.66 (d, J=7.8Hz, 1H)

mp: 214℃

Preparation 60

3-Chloro-2-isopropylsulfonylamino-6-trifluoromethylquinoxaline

IR (KBr) : 1562, 1460, 1437, 1325 cm^{-1}

1H NMR (DMSO-d_6, δ) : 1.39 (d, J=6.9Hz, 6H), 4.01 (m, 1H), 8.00-8.16 (m, 2H), 8.28 (broad s, 1H).

APCI-MS (m/z) : 354 (MH^+)

mp : 159℃

Preparation 61

2,6-Dichloro-3-isopropylsulfonylamino-7-nitroquinoxaline

IR (KBr) : 1541, 1444, 1346, 1146, 1072, 849 cm^{-1}

1H NMR (DMSO-d_6, δ) : 1.36 (d, J=6.8Hz, 6H), 4.03 (m, 1H), 8.30 (s, 1H), 8.65 (s, 1H)

FAB-MS (m/z) : 365 (M^+)

mp : 229~230℃

Preparation 62

2-Butylsulfonylamino-3-chloro-6-nitroquinoxaline

IR (KBr) : 3248, 1558, 1527, 1459, 1425, 1340, 1164 cm^{-1}

1H NMR (DMSO-d_6, δ) : 0.89 (t, J=7.3Hz, 3H), 1.44 (m, 2H), 1.77 (m, 2H), 3.66 (m, 2H), 8.10 (d, J=9.2Hz, 1H), 8.49 (d, J=9.2, 2.6Hz, 1H), 8.71 (d, J=2.5Hz, 1H)

FAB-MS (m/z) : 345(M^+)

mp : 170℃

Example 1

A suspension of 3-chloro-2-methylsulfonylamino-6-nitroquinoxaline (3.03 g) in acetic acid (30 ml) was refluxed under nitrogen atmosphere for 90 minutes, and the resulting solution was cooled to 20°C. To the reaction mixture, ethyl acetate (60 ml) was added. After stirred under ice-cooling for 30 minutes, the resulting precipitate was collected by filtration and washed with ethyl acetate and dried in vacuo

to give 3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (1.76 g).

IR (KBr) : 1673 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.43 (s, 3H), 7.79 (d, J=9.6Hz, 1H), 8.03-8.07 (m, 2H), 11.23 (bs, 1H), 12.85 (bs, 1H)

APCI-MS (m/z) : 285 (MH^+)

mp : 251°C

Example 2

A suspension of 2-chloro-6-fluoro-3-methylsulfonylamino-7-nitroquinoxaline (962 mg) in acetic acid (14.4 ml) was refluxed under nitrogen atmosphere for 3 hours, and the resulting solution was cooled to 20°C. To the reaction mixture, cold water (72 ml) was added. After stirred in an ice bath for 15 minutes, the resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 6-fluoro-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (780 mg).

IR (KBr) : 1676 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.44 (s, 3H), 7.78 (d, J=12.3Hz, 1H), 7.95 (d, J=7.2Hz, 1H), 12.80 (bs, 1H)

APCI-MS (m/z) : 303 (MH^+)

mp : 274°C

The following compounds (Examples 3 to 10) were obtained according to substantially the similar manner to those of Examples 1 and 2.

Example 3

6-Chloro-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (1.76 g).

IR (KBr) : 1680 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.44 (s, 3H), 7.78 (s, 1H), 7.95 (s, 1H), 11.23 (bs, 1H), 12.86 (bs, 1H)

APCI-MS (m/z) : 319 (MH^+)
mp : 258-260°C

Example 4

3-Methylsulfonylamino-7-trifluoromethyl-2(1H)-quinoxalinone (1.16 g).
IR (KBr) : 1695 cm^{-1}
1H NMR (DMSO-d_6, δ) : 3.44 (s, 3H), 7.54 (s, 1H), 7.56 (d, J=8.2Hz, 1H), 7.79 (d, J=8.2Hz, 1H), 10.97 (bs, 1H), 12.82 (bs, 1H)
APCI-MS (m/z) : 308 (MH^+)
mp : 208-209°C

Example 5

3-Methylsulfonylamino-6-methoxy-7-nitro-2(1H)-quinoxalinone (172 mg).
IR (KBr) : 1674 cm^{-1}
1H NMR (DMSO-d_6, δ) : 3.43 (s, 3H), 3.96 (s, 3H), 7.50 (s, 1H), 7.76 (s, 1H), 11.10 (bs, 1H), 12.60 (bs, 1H)
APCI-MS (m/z) : 315 (MH^+)
mp : 266°C

Example 6

7-Nitro-3-sulfamido-2(1H)-quinoxalinone (385 mg).
IR (KBr) : 1695 cm^{-1}
1H NMR (DMF-d_7+D_2O, δ) : 7.66 (d, J=8.9Hz, 1H), 7.66 (dd, J=8.9Hz, 2.5Hz, 1H), 8.31 (d, J=2.5Hz, 1H)
FAB-MS (m/z) : 285 (M^+)
mp : 251-253°C

Example 7

3-[(N-Methyl)methylsulfonylamino]-7-nitro-2(1H)-quinoxalinone (85 mg).
IR (KBr) : 1674 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.35 (s, 3H), 3.60 (s, 3H), 7.89 (d, J=9.0Hz, 1H), 8.08 (dd, J=9.0Hz, 2.5Hz, 1H), 8.11 (d, J=2.5Hz, 1H)

FAB-MS (m/z) : 299 (MH^+)

mp : 233°C (decomp.)

Example 8

3-Isopropylsulfonylamino-7-nitro-2(1H)-quinoxalinone (526 mg).

IR (KBr) : 1713, 1616, 1537, 1340 cm^{-1}

1H NMR (DMSO-d_6, δ) : 1.35 (d, J=6.8Hz, 6H), 4.08 (m, 1H), 7.77 (d, J=8.1Hz, 1H), 8.03 (m, 2H).

APCI-MS (m/z) : 313 (MH^+)

mp : >280°C

Example 9

3-Octylsulfonylamino-7-nitro-2(1H)-quinoxalinone (347 mg).

IR (KBr) : 1691, 1610, 1579, 1531, 1344 cm^{-1}

1H NMR (DMSO-d_6, δ) : 0.81 (m, 3H), 1.05-1.55 (m, 10H), 1.71 (m, 2H), 3.63 (m, 2H), 7.77 (d, J=9.2Hz, 1H), 8.04 (m, 2H), 11.12 (m, 1H), 12.89 (m, 1H).

APCI-MS (m/z) : 383 (MH^+)

mp : 186°C

Example 10

3-(3-Pyridyl)sulfonylamino-7-nitro-2(1H)-quinoxalinone (66 mg).

IR (KBr) : 1678, 1525, 1481, 1344 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.64-7.79 (m, 2H), 8.00 (s, 1H), 8.05 (m, 1H), 8.50 (d, J=8.2Hz, 1H), 8.83 (d, J=4.1Hz, 1H), 9.24 (s, 1H), 12.8 (s, 1H).

APCI-MS (m/z) : 348 (MH^+)

mp : >280°C

Example 11

A mixture of 2-methylsulfonylamino-6-nitroquinoxaline (4.02 g) and monoperoxyphthalic acid magnesium salt hexahydrate (22.3 g) in acetic acid (80 ml) was stirred at 70°C under nitrogen atmosphere for 6 hours. After cooled to room temperature, the resulting precipitate was removed by filtration, and the filtrate was poured into a mixture of ethyl acetate (300 ml) and water (300 ml). The separated organic layer was washed with brine. A mixture of the organic layer and water (200 ml) was adjusted to pH 7 with 4 M sodium hydroxide solution, and then a mixture of the separated aqueous layer and ethyl acetate (200 ml) was adjusted to pH 2 with 6 M hydrochloric acid. The organic layer was washed with brine and dried over magnesium sulfate and evaporated. The residue was triturated with a mixture of isopropyl ether (40 ml) and methanol (10 ml), and the resulting precipitate was collected by filtration, and washed with a mixture of isopropyl ether and methanol, and dried in vacuo to give 3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (1.18 g).

IR (KBr) : 1701, 1576, 1535, 1481, 1442, 1344, 1147 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.43 (s, 3H), 7.79 (d, J=9.6Hz, 1H), 8.02-8.07 (m, 2H), 12.84 (bs, 1H)

APCI-MS (m/z) : 285 (MH^+)

mp : 251°C

The following compounds (Examples 12 to 14) were obtained according to substantially the similar manner to that of Example 11.

Example 12

7-Dimethylaminosulfonyl-3-methylsulfonylamino-2(1H)-quinoxalinone (220 mg).

IR (KBr) : 1674, 1479, 1329, 1155, 972, 845, 716 cm-1

1H NMR (DMSO-d_6, δ) : 2.63 (s, 6H), 3.42 (s, 3H), 7.53-7.62 (m, 2H), 7.80-7.84 (m, 1H), 11.05 (bs, 1H) ,

12.80 (bs, 1H)

APCI-MS (m/z) : 347 (MH^+)

mp : 263-264°C

Example 13

3-Phenylsulfonylamino-7-nitro-2(1H)-quinoxalinone (180 mg).

IR (KBr) : 1695, 1525, 1481,1342, 1162 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.59-8.15 (m, 8H), 12.78 (bs, 1H)

APCI-MS (m/z) : 347 (MH^+)

mp : 226-227°C (decomp.)

Example 14

3-Methylsulfonylamino-2(1H)-quinoxalinone (704 mg).

IR (KBr) : 1682, 1578, 1493, 1439, 1333, 1144, 756 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.44 (s, 3H), 7.10-7.65 (m, 4H), 10.55 (bs, 1H), 12.64 (bs, 1H)

APCI-MS (m/z) : 240(MH^+)

mp : 248°C

Example 15

To a suspension of 3-methylsulfonylamino-6-nitro-2(1H)-quinoxalinone (284 mg) in conc. sulfuric acid (2.8 ml) was added nitric acid (fuming, d=1.52)(0.12 ml) at 0-10°C. After stirred at 40-50°C under nitrogen atmosphere for 7 hours, the reaction mixture was poured into cold water (50 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 3-methylsulfonylamino-6,8-dinitro-2(1H)-quinoxalinone (190 mg).

IR (KBr) : 1709, 1628, 1539, 1493, 1435, 1340, 1146 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.48 (s, 3H), 8.69 (d, J=2.5Hz, 1H), 8.88 (d, J=2.5Hz, 1H)

FAB-MS (m/z) : 330 (MH^+)

mp : 235°C

Example 16

To a suspension of 3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (1.28 g) in conc. sulfuric acid (13 ml) was added nitric acid (fuming, d=1.52)(0.56 ml) at 0-10°C. After stirred at 0-10°C under nitrogen atmosphere for 30 minutes and at room temperature for 20 hours, the reaction mixture was poured into cold water (130 ml) and stirred in an ice bath for one hour. The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 3-methylsulfonylamino-6,7-dinitro-2(1H)-quinoxalinone (711 mg).

IR (KBr) : 1686, 1547, 1331, 1159, 858 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.46 (s, 3H), 7.85 (s, 1H), 8.40 (s, 1H), 13.16 (bs, 1H)

FAB-MS (m/z) : 330 (MH^+)

mp : 244-245°C

Example 17

To a suspension of 3-methylsulfonylamino-7-trifluoromethyl-2(1H)-quinoxalinone (615 mg) in conc. sulfuric acid (6.15 ml) was added nitric acid (fuming, d=1.52)(0.10 ml) at 0-10°C. After stirred under nitrogen atmosphere for 2 hours at 0-10°C and for one hour at room temperature, the reaction mixture was poured into cold water (50 ml) and stirred in an ice bath for 30 minutes. The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 3-methylsulfonylamino-6-nitro-7-trifluoromethyl-2(1H)-quinoxalinone (660 mg).

IR (KBr) : 1697 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.45 (s, 3H), 7.69 (s, 1H), 8.42 (s, 1H), 13.10 (bs, 1H)

APCI-MS (m/z) : 353 (MH^+)

mp : 225°C

Example 18

To a suspension of 3-methylsulfonylamino-2(1H)-quinoxalinone (598 mg) in conc. sulfuric acid (6 ml) was added potassium nitrate (278 mg) at 0-5°C. After stirred at room temperature under nitrogen atmosphere for 3 hours, the resulting solution was poured into ice-water (60 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 3-methylsulfonylamino-6-nitro-2(1H)-quinoxalinone (630 mg).

IR (KBr) : 1695, 1622, 1587, 1543, 1325, 1153, 858 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.46 (s, 3H), 7.40 (d, J=8.9Hz, 1H), 8.20-8.26 (m, 1H), 8.40 (bs, 1H), 11.05 (bs, 1H), 13.07 (bs, 1H)

APCI-MS (m/z) : 285 (MH^+)

mp : 267-268°C

Example 19

A solution of 6-fluoro-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (302 mg) and imidazole (204 mg) in N,N-dimethylformamide (6 ml) was stirred at 140°C under nitrogen atmosphere for 20 hours, and then cooled to 20°C and poured into a mixture of cold water (60 ml) and ethyl acetate (60 ml). After adjusted to pH 3 with 6M hydrochloric acid, the resulting precipitate was collected by filtration, and washed with water and ethyl acetate, and dried in vacuo to give 6-(1-imidazolyl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (250 mg).

IR (KBr) : 1680 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.67 (s, 3H), 7.22 (s, 1H), 7.54 (s, 1H), 7.78 (s, 1H), 7.98 (s, 1H), 8.18 (s, 1H)

FAB-MS (m/z) : 351 (M^+)

mp : >280°C

The following compounds (Examples 20 to 30) were obtained according to substantially the similar manners to those of Examples 1 and 2.

Example 20

3-Methylsulfonylamino-7-nitro-6-trifluoromethoxy-2(1H)-quinoxalinone

IR (KBr): 1698, 1579, 1541, 1487, 1446 cm^{-1}

1H NMR (DMSO-d_6, δ): 3.44 (s, 3H), 7.90 (s, 1H), 7.97 (s, 1H), 12.90 (broad s, 1H).

APCI-MS (m/z): 369 (MH^+)

mp: 275℃ (decomp.)

Example 21

7-Cyano-3-methylsulfonylamino-2(1H)-quinoxalinone

IR (KBr): 1687, 1614, 1572, 1483, 1440 cm^{-1}

1H NMR (DMSO-d_6, δ): 3.42 (s, 3H), 7.57 (d, J=1.7Hz, 1H), 7.64 (dd, J=8.3, 1.7Hz, 1H), 7.75 (d, J=8.3Hz, 1H), 11.06 (broad s, 1H), 12.77 (broad s, 1H).

FAB-MS (m/z): 265 (MH^+)

mp: 287℃ (decomp.)

Example 22

3-Methylsulfonylamino-6-methyl-7-nitro-2(1H)-quinoxalinone

IR (KBr): 1687, 1578, 1529, 1333 cm^{-1}

1H NMR (DMSO-d_6, δ): 2.57 (s, 3H), 3.42 (s, 3H), 7.70 (s, 1H), 7.89 (s, 1H), 11.10 (bs, 1H), 12.72 (bs, 1H)

APCI-MS (m/z): 299 (MH^+)

mp: 264~265℃

Example 23

3-Ethylsulfonylamino-7-nitro-2(1H)-quinoxalinone

IR (KBr): 1712, 1639, 1618, 1342 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.28 (t, J=7.3Hz, 3H), 3.61 (m, 2H), 7.77 (d, J=9.5Hz, 1H), 8.04 (m, 2H)

APCI-MS (m/z): 299(MH^+)

mp: 255℃

Example 24

6-Fluoro-3-ethylsulfonylamino-7-nitro-2(1H)-quinoxalinone

IR (KBr): 1682, 1576, 1531, 1493, 1443, 1406, 1342, 1144, 849 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.27 (t, J=7.4Hz, 3H), 3.61 (q, J=7.4Hz, 2H), 7.25 (d, J=12.3Hz, 1H), 7.95 (d, J=7.2Hz, 1H), 12.75 (bs, 1H)

APCI-MS (m/z): 317 (MH^+)

mp: 117~118℃

Example 25

3-Propylsulfonylamino-7-nitro-2(1H)-quinoxalinone

IR (KBr): 1711, 1616, 1537, 1344 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.00 (t, J=7.4Hz, 3H), 1.77 (m, 2H), 3.59 (m, 2H), 7.78 (d, J=9.5Hz, 1H), 8.04 (m, 2H).

FAB-MS (m/z): 313(M^+)

mp: 269℃

Example 26

6-Fluoro-3-propylsulfonylamino-7-nitro-2(1H)-quinoxalinone

IR (KBr): 1686, 1574, 1539, 1489, 1431, 1335, 1147, 840 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.00(t, J=7.5Hz, 3H), 1.61~1.91(m, 2H), 3.50~3.70(m, 2H), 7.76(d, J=12.3Hz, 1H), 7.94(d, J=7.2Hz, 1H), 12.76(bs, 1H)

APCI-MS (m/z): 331 (MH^+)

mp: 230 ℃

Example 27

6-Fluoro-3-isopropylsulfonylamino-7-nitro-2(1H)-quinoxalinone

IR (KBr): 1714, 1545, 1435, 1331, 1138 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.34 (d, J=6.8Hz, 6H), 4.00 (m, 1H), 7.76 (d, J=12.3Hz, 1H), 7.94 (d, J=7.2Hz, 1H), 11.22 (bs, 1H), 12.72 (bs, 1H)

APCI-MS (m/z): 331 (MH^+)

mp: >280 ℃

Example 28

3-Isopropylsulfonylamino-7-trifluoromethyl-2(1H)-quinoxalinone

IR (KBr): 1709, 1639, 1612, 1236 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.34 (d, J=6.8Hz, 6H), 4.07 (m, 1H), 7.53 (m, 2H), 7.78 (d, J=8.8Hz, 1H)

APCI-MS (m/z): 336 (MH^+)

mp: 259℃

Example 29

6-Chloro-3-isopropylsulfonylamino-7-nitro-2(1H)-quinoxalinone

IR (KBr): 1701, 1537, 1342, 1140 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.33 (d, J=6.8Hz, 6H), 4.10 (m, 1H), 7.86 (d, J=12.3Hz, 1H), 7.93 (d, J=7.2Hz, 1H), 12.83 (bs, 1H)

APCI-MS (m/z): 347 (MH^+)

mp: 277 ℃

Example 30

3-Butylsulfonylamino-7-nitro-2(1H)-quinoxalinone

IR (KBr): 1713, 1616, 1537, 1344 cm^{-1}

1H NMR (DMSO-d_6, δ): 0.88 (t, J=7.2Hz, 3H), 1.42 (m, 2H), 1.73 (m, 2H), 3.62 (m, 2H), 7.77 (d, J=9.6Hz, 1H), 8.04 (m, 2H).

APCI-MS (m/z): 327 (MH^+)

mp: 228℃

Example 31

To a suspension of sodium hydride (60% oil dispersion, 160 mg) in N,N-dimethylformamide (10 ml) was added trifluoromethanesulfonamide (298.2 mg) at 0~5℃ under nitrogen atmosphere, and the mixture was stirred at room temperature for 15 minutes. 2,3-Dichloro-6-nitroquinoxaline (488 mg) was added to the mixture at 0~5℃, and the resulting solution was stirred for 3 hours with warming up to room temperature and then poured into a mixture of cold water (150 ml) and ethyl acetate (150 ml). The organic layer was washed with brine, 0.5N-HCl, and brine, and dried over magnesium sulfate, and evaporated. A solution of the residue in acetic acid (10 ml) was refluxed for 3 hours and cooled in an ice bath. To the mixture was added 50 ml of water, and the mixture was stirred for 15 minutes at 5℃. The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 7-nitro-3-trifluoromethylsulfonylamino-2(1H)-quinoxalinone (154 mg).

IR (KBr) : 1716, 1628, 1606, 1529, 1344 cm-1

1H NMR (DMSO-d_6, δ) : 7.55 (d, J=8.7Hz, 1H), 7.96-8.08 (m, 2H), 12.78 (broad s, 1H).

FAB-MS (m/z) : 339 (MH^+)

Example 32

A solution of 6-fluoro-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (604 mg) and 2-methylimidazole (821 mg) in 1,3-dimethyl-2-imidazolidinone (6 ml) was stirred at 140℃ under nitrogen atmosphere for 14 hours, and then cooled to 20℃ and poured into ethyl acetate (90 ml). The resulting precipitate was collected by filtration and washed with ethyl acetate to give crude product. The product was recrystallized from 1,3-dimethyl-2-imidazolidinone/water to give 6-(2-methyl-1-imidazolyl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (214 mg).

IR (KBr) : 1668, 1661, 1510, 1477, 1325, 1225, 1088, 780, 872 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.34 (s, 3H), 3.29 (s, 3H), 7.46 (d, J=1.7Hz, 1H), 7.59 (d, J=1.7Hz, 1H), 7.81 (s, 1H), 8.07 (s, 1H)
FAB-MS (m/z) : 365 (MH^+)
mp : >280℃

Example 33

A solution of 6-fluoro-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (604 mg) and 4-methylimidazole (821 mg) in 1,3-dimethyl-2-imidazolidinone (6 ml) was stirred at 140℃ under nitrogen atmosphere for 12 hours, and then cooled to 20℃ and poured into ethyl acetate (90 ml). The resulting precipitate was collected by filtration and washed with ethyl acetate to give crude product. Recrystallization of the crude product from 1,3-dimethyl-2-imidazolidinone/water gave 6-(4-methyl-1-imidazolyl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (61 mg) and 6-(5-methyl-1-imidazolyl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (39 mg).

(1) 6-(4-Methyl-1-imidazolyl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone
IR (KBr) : 1674, 1618, 1512, 1471, 1321, 1261, 1103, 970, 854 cm^{-1}
1H NMR (DMSO-d_6, δ) : 2.20 (s, 3H), 3.33 (s, 3H), 7.25 (d, J=1.3Hz, 1H), 7.72 (s, 1H), 7.95 (s, 1H), 8.17 (d, J=1.3Hz, 1H)
FAB-MS (m/z) : 365 (MH^+)
mp : >280℃

(2) 6-(5-Methyl-1-imidazolyl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone
IR (KBr) : 1682, 1522, 1479, 1321, 1255, 1111, 976, 868 cm^{-1}
1H NMR (DMSO-d_6, δ) : 2.01 (s, 3H), 3.29 (s, 3H), 7.08 (s, 1H), 7.70 (s, 1H), 8.02 (s, 1H),

8.21 (s, 1H)

FAB-MS (m/z) : 365 (MH^+)

mp : >280℃

The following compounds (Examples 34 and 35) were obtained according to substantially the similar manner to that of Example 19.

Example 34

6-(1-Imidazolyl)-3-ethylsulfonylamino-7-nitro-2(1H)-quinoxalinone (280 mg).

IR (KBr) : 1680, 1516, 1475, 1323, 1109 cm^{-1}

1H NMR (DMSO-d_6, δ) : 1.24 (t, J=7.4Hz, 3H), 3.59 (q, J=7.4Hz, 2H), 7.18 (s, 1H), 7.50 (s, 1H), 7.79 (s, 1H), 7.98 (s, 1H), 8.09 (s, 1H)

APCI-MS (m/z) : 365 (MH^+)

mp : >280℃

Example 35

6-(1-Imidazolyl)-3-propylsulfonylamino-7-nitro-2(1H)-quinoxalinone (747 mg).

IR (KBr) : 1682, 1518, 1475, 1327, 1111 cm^{-1}

1H NMR (DMSO-d_6, δ) : 0.98 (t, J=7.4Hz, 3H), 1.74 (m, 2H), 3.56 (m, 2H), 7.18 (s, 1H), 7.50 (s, 1H), 7.80 (s, 1H), 7.98 (s, 1H), 8.09 (s, 1H)

APCI-MS (m/z) : 379 (MH^+)

mp : 276℃

Example 36

6 ml of Nitric acid (fuming) was added to 7-cyano-3-methylsulfonylamino-2(1H)-quinoxalinone (132 mg) at 5℃. After stirred at room temperature under nitrogen atmosphere for 48 hours, the resulting solution was poured into ice-water (60 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give

7-cyano-3-methylsulfonylamino-6-nitro-2(1H)-quinoxalinone (48 mg).

IR (KBr): 1709, 1639, 1610, 1542, 1336 cm^{-1}

1H NMR (DMSO-d_6, δ): 3.45 (s, 3H), 7.69 (s, 1H), 8.53 (s, 1H), 13.11 (broad s, 1H)

FAB-MS (m/z): 310 (MH^+)

mp: >280℃

Example 37

To a suspension of 3-isopropylsulfonylamino-7-nitro-2(1H)-quinoxalinone (192 mg) in conc. sulfuric acid (5 ml) was added 0.08 ml of nitric acid (fuming) at 0~5℃. After stirred at 50℃ under nitrogen atmosphere for 2 hours, the resulting solution was poured into ice-water (100 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 3-isopropylsulfonylamino-6,7-dinitro-2(1H)-quinoxalinone (113 mg).

IR (KBr): 1702, 1620, 1583, 1547, 1495, 1450, 1338 cm^{-1}

1H NMR (DMSO-d_6, δ): 1.34 (d, J=6.8Hz, 6H), 4.07 (m, 1H), 7.83 (s, 1H), 8.39 (s, 1H)

FAB-MS (m/z): 358 (MH^+)

mp: 253℃

Example 38

To a suspension of 3-isopropylsulfonylamino-7-trifluoromethyl-2(1H)-quinoxalinone (353 mg) in conc. sulfuric acid (5 ml) was added 0.12 ml of nitric acid (fuming) at 0~5℃. After stirred at room temperature under nitrogen atmosphere for 2 hours, the resulting solution was poured into ice-water (200 ml). The resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 3-isopropylsulfonylamino-6-nitro-7-trifluoromethyl-2(1H)-quinoxalinone (318 mg).

IR (KBr): 1693, 1626, 1581, 1547, 1500, 1346 cm^{-1}

1H NMR (DMSO-d_6, δ) : 1.34 (d, J=6.8Hz, 6H), 4.06 (m, 1H), 7.68 (s, 1H), 8.41 (broad s, 1H)

FAB-MS (m/z) : 345 (M^+)

mp : 163℃ (decomp.)

Preparation 63

To a stirred solution of 3-hydroxy-2-methyl-4-pyrone (12.6 g) in DMF (N,N-dimethylformamide) (200 ml) were added p-methoxybenzyl chloride (13.5 ml) and K_2CO_3 (13.8 g) at room temperature and the mixture was stirred at 40°C for 18 hours. The mixture was extracted with EtOAc, and the extract was washed with water and dried over $MgSO_4$. The oily residue was dissolved in EtOH (20 ml) and ammonia solution (28%, 200ml) was added. The reaction mixture was refluxed with stirring for 12 hours. It was then concentrated under reduced pressure to an oil, which was dissolved into water (500 ml) and adjusted to pH 3.5 with 6N-HCl. The resultant precipitate was collected by filtration and washed with water to give crude product which was chromatographed on silica gel with CH_2Cl_2-MeOH (10:1) to give 2-methyl-3-(4-methoxybenzyloxy)-4-pyridone (5.56 g).

1H NMR (DMSO-d_6, δ) : 2.05 (s, 3H), 3.74 (s, 3H), 4.99 (s, 2H), 6.25 (d, J=7.3Hz, 1H), 6.90 (m, 2H), 7.30 (m, 2H), 7.51 (d, J=7.3Hz, 1H)

APCI-MS (m/z) : 246 (MH^+)

Preparation 64

By a procedure identical with that described in Example 41, 6-fluoro-7-nitro-2,3-(1H,4H)-quinoxalinedione (3.38 g) was converted into 6-(2-dimethylaminoethylthio)-7-nitro-2,3 (1H,4H)-quinoxalinedione (4.72 g) by treatment with KOH (86%, 3.18 g), and 2-(dimethylamino)ethanethiol hydrochloride (4.781 g) in DMSO (80 ml) at 120°C for 2 hours.

1H NMR (DMSO-d_6, δ) : 2.37 (s, 6H), 2.78 (m, 2H), 3.14 (m, 2H), 7.28 (s, 1H), 7.99 (s, 1H), 12.04 (broad

s, 2H)

APCI-MS (m/z) : 311 (MH^+)

Preparation 65

A mixture of 6-fluoro-7-nitro-2,3(1H,4H)-quinoxalinedione (4.50 g), 4-mercaptopyridine (2.45 g), and powdered potassium carbonate (3.04 g) in N,N-dimethylformamide (67.5 ml) was stirred at 120°C under nitrogen atmosphere for 3 hours, and then cooled to 15°C and poured into cold water (340 ml). The mixture was adjusted to pH 7 with 1M hydrochloric acid, and the resulting precipitate was collected by filtration and washed with ethyl acetate. The suspension of the precipitate in water (50 ml) was adjusted to pH 2 with 1M hydrochloric acid, and the precipitate was collected by filtration. The suspension of the precipitate in water (50 ml) was adjusted to pH 6.5 with 1M aqueous sodium hydroxide, and the precipitate was collected by filtration and washed with water and dried in vacuo to give 7-nitro-6-(pyridin-4-ylthio)-2,3(1H,4H)-quinoxalinedione (4.60 g).

IR (KBr) : 1707, 1578, 1527, 1500, 1387, 1338, 1302 cm^{-1}

1H NMR (DMSO-d_6, δ) : 6.93 (s, 1H), 7.46 (dd, J=4.5Hz and 1.6Hz, 2H), 7.96 (s, 1H), 8.63 (dd, J=4.5Hz and 1.6Hz, 2H), 12.14 (broad s, 1H)

FAB-MS (m/z) : 317 (MH^+)

mp : >280°C

Preparation 66

A mixture of 6-fluoro-7-nitro-2,3(1H,4H)-quinoxalinedione (2.25 g) and sodium thiomethoxide (2.50 g) in 1,3-dimethyl-2-imidazolidinone (23 ml) was stirred at 80°C under nitrogen atmosphere for 4 hours, and then poured into cold water (200 ml). The mixture was adjusted to pH 3 with 1M hydrochloric acid, and the resulting precipitate was

collected by filtration and dried in vacuo. The precipitate was recrystalized from N,N-dimethylformamide (40 ml) to give 6-methylthio-7-nitro-2,3(1H,4H)-quinoxalinedione (1.35 g).

IR (KBr) : 1724, 1686, 1525, 1392, 1308 cm^{-1}

1H NMR (DMF-d_7, δ) : 2.55 (s, 3H), 7.35 (s, 1H), 8.24 (s, 1H), 12.08 (broad s, 2H)

APCI-MS (m/z) : 254 (MH^+)

mp : >280°C

Preparation 67

A mixture of 6-fluoro-7-nitro-2,3(1H,4H)-quinoxalinedione (2.25 g), dimethylamine (50% solution in water, 1.80 ml), and N,N-dimethylformamide (23 ml) was stirred at 80°C under nitrogen atmosphere for 2 hours, and then cooled to 10°C and poured into cold water (160 ml). The mixture was adjusted to pH 6 with 1M hydrochloric acid and stirred in an ice-bath for 30 minutes. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give 6-dimethylamino-7-nitro-2,3(1H,4H)-quinoxalinedione (2.45 g).

IR (KBr) : 1691, 1639, 1541, 1385, 1288 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.76 (s, 6H), 6.83 (s, 1H), 7.65 (s, 1H), 11.83 (broad s, 1H), 12.01 (broad s, 1H)

APCI-MS (m/z) : 251 (MH^+)

mp : >280°C

Preparation 68

A mixture of 6-fluoro-7-nitro-2,3(1H,4H)-quinoxalinedione (3.38 g), 1-methylpiperazine (3.33 ml), and 1,3-dimethyl-2-imidazolidinone (30.4 ml) was stirred at 120°C under nitrogen atmosphere for 2 hours, and then cooled to 20°C and poured into diisopropyl ether (150 ml). The solvent was decanted and the oily residue was suspended in water (150 ml). The mixture was adjusted to pH 2 with 1M hydrochloric acid, and then adjusted to pH 5 with 1M sodium hydroxide.

After stirred in an ice-bath for 30 minutes, the resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give 6-(4-methylpiperazin-1-yl)-7-nitro-2,3(1H,4H)-quinoxalinedione hydrochloride (5.40 g).

IR (KBr) : 1695, 1630, 1545, 1497, 1389, 1292 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.83 (s, 3H), 3.10-3.60 (m, 8H), 7.03 (s, 1H), 7.80 (s, 1H), 12.04 (broad s, 1H), 12.17 (broad s, 1H)

APCI-MS (m/z) : 306 (MH^+)

mp : >260°C (decomp.)

The following compounds (Preparations 69 to 73) were obtained according to a similar manner to that of Preparation 16.

Preparation 69

6-(2-Dimethylaminoethylthio)-7-nitro-2,3-dichloroquinoxaline

1H NMR (DMSO-d_6, δ) : 2.83 (s, 6H), 3.54 (m, 2H), 3.68 (m, 2H), 8.33 (s, 1H), 8.88 (s, 1H)

FAB-MS (m/z) : 384 (MH^+)

Preparation 70

2,3-Dichloro-7-nitro-6-(pyridin-4-ylthio)quinoxaline hydrochloride

IR (KBr) : 1612, 1522, 1477, 1346, 1153, 1007, 806 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.74 (d, J=5.2Hz, 2H), 8.47 (s, 1H), 8.69 (d, J=5.2Hz, 2H), 9.01 (s, 1H)

APCI-MS (m/z) : 353 (MH^+)

mp : 256-260°C

Preparation 71

2,3-Dichloro-6-methylthio-7-nitroquinoxaline

IR (KBr) : 1605, 1527, 1348, 1261, 1153, 1012 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.70 (s, 3H), 8.07 (s, 1H),

8.86 (s, 1H)
APCI-MS (m/z) : 290 (MH^+)
mp : 225°C (decomp.)

Preparation 72

2,3-Dichloro-6-dimethylamino-7-nitroquinoxaline
IR (KBr) : 1616, 1539, 1510, 1387, 1269, 1165, 1134, 1009 cm^{-1}
1H NMR (DMSO-d_6, δ) : 2.94 (s, 6H), 7.48 (s, 1H), 8.49 (s, 1H)
APCI-MS (m/z) : 287 (MH^+)
mp : 256-260°C

Preparation 73

2,3-Dichloro-6-(4-methylpiperazin-1-yl)-7-nitroquinoxaline hydrochloride
IR (KBr) : 1616, 1531, 1458, 1286, 1223, 1142, 1011, 982, 523 cm^{-1}
1H NMR (DMSO-d_6, δ) : 2.89 (s, 3H), 3.0-3.7 (m, 8H), 7.92 (s, 1H), 8.67 (s, 1H), 10.10 (broad s, 1H)
APCI-MS (m/z) : 342 (MH^+)
mp : 242-244°C (decomp.)

The following compounds (Preparations 74 to 80) were obtained according to substantially the similar manner to those of Preparations 22 to 24.

Preparation 74

2-Chloro-6-(2-dimethylaminoethylthio)-3-methylsulfonylamino-7-nitroquinoxaline
1H NMR (DMSO-d_6, δ) : 2.82 (s, 6H), 3.36 (m, 2H), 3.45 (s, 3H), 3.65 (m, 2H), 8.03 (s, 1H), 8.66 (s, 1H), 10.72 (broad s, 1H)
APCI-MS (m/z) : 406 (MH^+)

Preparation 75

2-Chloro-3-methylsulfonylamino-7-nitro-6-(pyridin-4-ylthio)quinoxaline

IR (KBr) : 1527, 1471, 1329, 1151 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.20 (s, 3H), 7.67 (d, J=6.6Hz, 2H), 7.87 (s, 1H), 8.6-8.7 (m, 3H)

APCI-MS (m/z) : 412 (MH^+)

mp : 242-245°C (decomp.)

Preparation 76

2-Chloro-3-methylsulfonylamino-6-methylthio-7-nitroquinoxaline

IR (KBr) : 1605, 1554, 1524, 1446, 1323, 1159, 1074, 976, 858 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.65 (s, 3H), 3.20 (s, 3H), 7.87 (s, 1H), 8.64 (s, 1H)

APCI-MS (m/z) : 349 (MH^+)

mp : >280°C

Preparation 77

2-Chloro-6-dimethylamino-3-methylsulfonylamino-7-nitroquinoxaline

IR (KBr) : 1620, 1531, 1462, 1375, 1155, 1070, 860 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.91 (s, 6H), 3.40 (s, 3H), 7.44 (s, 1H), 8.28 (s, 1H)

APCI-MS (m/z) : 346 (MH^+)

mp : 219-220°C (decomp.)

Preparation 78

2-Chloro-3-methylsulfonylamino-6-(4-methylpiperazin-1-yl)-7-nitroquinoxaline hydrochloride

IR (KBr) : 1618, 1533, 1462, 1348, 1151, 1074, 976, 856 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.86 (s, 3H), 3.0-4.2 (m, 8H), 3.38 (s, 3H), 7.62 (s, 1H), 8.42 (s, 1H), 10.6

(broad s, 1H)

APCI-MS (m/z) : 401 (MH^+)

mp : 214-216°C (decomp.)

Preparation 79

2-Chloro-6-fluoro-7-nitro-3-(pyridin-3-ylsulfonylamino)-quinoxaline

1H NMR (DMSO-d_6, δ) : 7.62 (d, J=12.9Hz, 1H), 7.89 (m, 1H), 8.44 (d, J=8.0Hz, 1H), 8.80 (m, 2H), 9.36 (s, 1H)

APCI-MS (m/z) : 384 (MH^+)

Preparation 80

2-Chloro-6-fluoro-7-nitro-3-trifluoromethylsulfonyl-aminoquinoxaline

1H NMR (DMSO-d_6, δ) : 7.56 (d, J=12.8Hz, 1H), 8.52 (d, J=7.9Hz, 1H)

Preparation 81

According to substantially the similar manner to that of Preparation 16, 1,4,7,8,9,10-hexahydro-9-methyl-6-nitropyrido[3,4-f]quinoxaline-2,3-dione (1.1 g) was converted into 2,3-dichloro-9-methyl-6-nitro-7,8,9,10-tetrahydropyrido-[3,4-f]quinoxaline (762 mg) by treatment with $POCl_3$ (20 ml) and DMF (3 ml) under reflux for 2 hours.

1H NMR (DMSO-d_6, δ) : 2.71 (m, 2H), 3.06 (m, 2H), 3.24 (s, 3H), 3.98 (s, 2H), 8.55 (s, 1H)

FAB-MS (m/z) : 314 (MH^+)

Preparation 82

According to substantially the similar manners to those of Preparations 22 to 24, the compound obtained in Preparation 81 (470 mg) was converted into 2-methylsulfonylamino-3-chloro-6-nitro-9-methyl-7,8,9,10-tetrahydropyrido[3,4-f]quinoxaline (458 mg) by treatment with

$MeSO_2NH_2$ (143 mg), NaH (120 mg) in DMF (8 ml) at 5°C for 2 hours.

1H NMR (DMSO-d_6, δ) : 3.07 (s, 3H), 3.22-3.62 (m, 4H), 3.32 (s, 3H), 4.64 (broad s, 2H), 8.24 (s, 1H)

FAB-MS (m/z) : 372 (MH^+)

Preparation 83

According to substantially the similar manner to that of Preparation 11, 1,4-dihydropyrido[3,2-f]quinoxaline-2,3-dione (6.4 g) was converted into 6-nitro-1,4-dihydropyrido[3,2-f]-quinoxaline-2,3-dione (6.45 g) by treatment with KNO_3 (3.34 g) and c.H_2SO_4 (64 ml) at room temperature for 4 hours.

1H NMR (DMSO-d_6, δ) : 7.75 (dd, J=8.7, 4.2Hz, 1H), 8.06 (s, 1H), 8.97 (dd, J=4.2, 1.3Hz, 1H), 9.12 (dd, J=8.7, 1.3Hz, 1H), 12.41 (m, 2H)

APCI-MS (m/z) : 259 (MH^+)

Preparation 84

According to substantially the similar manner to that of Preparation 16, 6-nitro-1,4-dihydropyrido[3,2-f]quinoxaline-2,3-dione (1.03 g) was converted into 2,3-dichloro-6-nitro-pyrido[3,2-f]quinoxaline (867 mg) by treatment with $POCl_3$ (10 ml) and DMF (1 ml) under reflux for 3 hours.

1H NMR (DMSO-d_6, δ) : 8.05 (dd, J=8.4, 4.4Hz, 1H), 8.95 (s, 1H), 9.25 (dd, J=4.4, 1.6Hz, 1H), 9.34 (dd, J=8.4, 1.6Hz, 1H)

FAB-MS (m/z) : 296 (MH^+)

Preparation 85

According to substantially the similar manners to those of Preparations 22 to 24, the compound obtained in Preparation 84 (530 mg) was converted into 2-methylsulfonylamino-3-chloro-6-nitro-pyrido[3,2-f]-quinoxaline (495 mg) by treatment with $MeSO_2NH_2$ (171 mg), NaH (144 mg) in DMF (8 ml) at 5°C for 2 hours.

1H NMR (DMSO-d_6, δ) : 3.14 (s, 3H), 7.84 (dd, J=8.3, 4.4Hz, 1H), 8.47 (s, 1H), 9.07 (dd, J=4.4, 1.8Hz, 1H), 9.21 (dd, J=8.3, 1.8Hz, 1H)

APCI-MS (m/z) : 354 (MH^+)

The following compounds (Examples 39 and 40) were obtained according to substantially the similar manner to that of Example 19.

Example 39

6-(1-Imidazolyl)-3-trifluoromethylsulfonylamino-7-nitro-2(1H)-quinoxalinone

1H NMR (DMSO-d_6, δ) : 7.69 (s, 1H), 7.84 (s, 1H), 8.03 (s, 2H), 9.42 (s, 1H), 12.38 (s, 1H)

APCI-MS (m/z) : 405 (MH^+)

Example 40

6-(1-Imidazolyl)-3-(3-pyridylsulfonylamino)-7-nitro-2(1H)-quinoxalinone

1H NMR (DMSO-d_6, δ) : 7.17 (s, 1H), 7.44 (m, 1H), 7.50 (s, 1H), 7.84 (s, 1H), 7.93 (s, 1H), 8.32 (m, 1H), 8.57 (dd, J=4.8, 1.6Hz, 1H), 8.68 (s, 1H), 9.06 (m, 1H)

APCI-MS (m/z) : 414 (MH^+)

Example 41

A stirred suspension of 6-fluoro-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (9.07 g), KOH (86%, 3.91 g), and 4-hydroxypyridine (4.28 g) in DMSO (90 ml) was heated at 120°C for 5 hours and then poured onto ice-water. The resulting solution was adjusted to pH 4.5 with 1N-HCl. The resultant precipitate was collected by filtration and washed with water, MeOH, and isopropyl ether to give 3-methylsulfonylamino-7-nitro-6-(4-oxo-1,4-dihydropyridin-1-yl)-2(1H)-quinoxalinone (11.2 g).

1H NMR (DMSO-d_6, δ) : 3.43 (s, 3H), 6.26 (d, J=7.6Hz, 2H), 7.86 (d, J=7.6Hz, 2H), 7.98 (s, 1H), 8.06 (s, 1H), 12.94 (broad s, 1H)

APCI-MS (m/z) : 378 (MH^+)

Anal. Calcd for $C_{14}H_{11}N_5O_6S_1$:

C 44.56, H 2.94, N 18.56

Found : C 44.66, H 2.78, N 18.21

The following compounds (Examples 42 to 45) were obtained according to substantially similar manner to that of Example 41.

Example 42

3-Methylsulfonylamino-7-nitro-6-(2-oxo-1,2-dihydropyridin-1-yl)-2(1H)-quinoxalinone

1H NMR (DMSO-d_6, δ) : 3.21 (s, 3H), 6.40 (m, 2H), 7.44 (s, 1H), 7.55 (m, 1H), 7.80 (dd, J=7.0, 1.6Hz, 1H), 7.90 (s, 1H), 12.30 (broad s, 1H)

APCI-MS (m/z) : 378 (MH^+)

Example 43

3-Methylsulfonylamino-7-nitro-6-(3-nitro-4-oxo-1,4-dihydropyridin-1-yl)-2(1H)-quinoxalinone

1H NMR (DMSO-d_6, δ) : 3.45 (s, 3H), 6.62 (d, J=8.0Hz, 1H), 8.01 (dd, J=8.0, 2.3Hz, 1H), 8.15 (s, 1H), 8.18 (s, 1H), 9.14 (d, J=8.0Hz, 1H), 13.03 (broad s, 1H)

APCI-MS (m/z) : 423 (MH^+)

Example 44

6-(3-Amino-4-oxo-1,4-dihydropyridin-1-yl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone acetate

1H NMR (DMSO-d_6, δ) : 1.71 (s, 3H), 3.02 (s, 3H), 4.67 (broad s, 2H), 6.07 (d, J=7.4Hz, 1H), 7.14 (d, J=2.4Hz, 1H), 7.24 (s, 1H), 7.52 (dd, J=7.4, 2.4Hz,

1H), 7.90 (s, 1H) 8.06 (s, 1H), 12.94 (broad s, 1H)
FAB-MS (m/z) : 393 (MH^+) (Free)

Example 45

6-[2-Methyl-3-(4-methoxybenzyloxy)-4-oxo-1,4-dihydropyridin-1-yl]-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone

1H NMR (DMSO-d_6, δ) : 2.31 (s, 3H), 2.99 (s, 3H), 3.75 (s, 3H), 5.06 (s, 2H), 6.60 (d, J=5.5Hz, 1H), 6.92 (m, 2H), 6.97 (s, 1H), 7.37 (m, 2H), 7.90 (s, 1H), 8.00 (d, J=5.5Hz, 1H), 11.92 (broad s, 1H)
FAB-MS (m/z) : 528 (MH^+)

Example 46

A solution of 6-[2-methyl-3-(4-methoxybenzyloxy)-4-oxo-1,4-dihydropyridin-1-yl]-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (30 mg) in TFA (3 ml) was stirred at 5°C for 1 hour. The reaction mixture was diluted with IPE. The resultant precipitate was collected by filtration and washed with IPE to give 3-methylsulfonylamino-7-nitro-6-(3-hydroxy-2-methyl-4-oxo-1,4-dihydropyridin-1-yl)-2(1H)-quinoxalinone (19 mg).

1H NMR (DMSO-d_6, δ) : 2.36 (s, 3H), 3.33 (s, 3H), 6.61 (d, J=7.0Hz, 1H), 7.04 (s, 1H), 7.86 (s, 1H), 7.97 (d, J=7.0Hz, 1H), 12.69 (broad s, 1H)
FAB-MS (m/z) : 408 (MH^+)

Example 47

A mixture of 2-chloro-6-dimethylamino-3-methylsulfonylamino-7-nitroquinoxaline (346 mg), trifluoroacetic acid (10.5 ml), and anisole (3.5 ml) was stirred under nitrogen atmosphere at room temperature for 24 hours, and then at 40°C for 30 minutes. The mixture was poured into diisopropyl ether (70 ml), and the resulting precipitate was collected by filtration and washed with

diisopropyl ether. The suspension of the precipitate in water (30 ml) was adjusted to pH 12 with 1M sodium hydroxide, and then resulting solution was adjusted to pH 3 with 1M hydrochloric acid. After stirred in an ice bath for 30 minutes, the resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give 6-dimethylamino-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (258 mg).

IR (KBr) : 1670, 1587, 1522, 1147, 1061, 984, 885 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.79 (s, 6H), 3.31 (s, 3H), 7.37 (broad s, 1H), 7.67 (s, 1H), 11.0 (broad s, 1H), 12.5 (broad s, 1H)

FAB-MS (m/z) : 328 (MH^+)

mp : 212 °C

Example 48

A mixture of 2-chloro-3-methylsulfonylamino-6-(4-methylpiperazin-1-yl)-7-nitroquinoxaline hydrochloride (437 mg) and trifluoroacetic acid (6.6 ml) was stirred under nitrogen atmosphere at room temperature for 24 hours. The mixture was poured into diisopropyl ether (66 ml), and the resulting precipitate was collected by filtration and washed with diisopropyl ether. The suspension of the precipitate in water (40 ml) was adjusted to pH 10 with 1M sodium hydroxide, and then resulting solution was adjusted to pH 1 with 1M hydrochloric acid. After stirred in an ice bath for 30 minutes, the resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give 3-methylsulfonylamino-6-(4-methylpiperazin-1-yl)-7-nitro-2(1H)-quinoxalinone hydrochloride (380 mg).

IR (KBr) : 1691, 1527, 1352, 1147, 984, 860 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.83 (s, 3H), 3.0-3.8 (m, 11H), 7.59 (broad s, 1H), 7.85 (s, 1H), 11.04 (broad s, 1H), 12.75 (broad s, 1H)

APCI-MS (m/z) : 383 (MH^+)

mp : 277-278 °C (decomp.)

The following compounds (Examples 49 and 50) were obtained according to substantially the similar manner to that of Example 48.

Example 49

6-(2-Dimethylaminoethylthio)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone

1H NMR (DMSO-d_6, δ) : 2.84 (s, 6H), 3.34 (m, 2H), 3.38 (s, 3H), 3.49 (m, 2H), 7.77 (s, 1H), 8.05 (s, 1H), 12.79 (broad s, 1H)

FAB-MS (m/z) : 388 (MH^+)

Example 50

6-Fluoro-7-nitro-3-trifluoromethylsulfonylamino-2(1H)-quinoxalinone

1H NMR (DMSO-d_6, δ) : 7.86 (d, J=11.9Hz, 1H), 7.91 (d, J=7.1Hz, 1H), 12.66 (broad s, 1H)

APCI-MS (m/z) : 357 (MH^+)

Example 51

A suspension of 2-chloro-3-methylsulfonylamino-6-methylthio-7-nitroquinoxaline (522 mg) in acetic acid (10.4 ml) was refluxed under nitrogen atmosphere for 3 hours, and the mixture was cooled to 20°C. The resulting precipitate was collected by filtration and washed with acetic acid and dried in vacuo. The suspension of the precipitate in water (60 ml) was adjusted to pH 11 with 1M sodium hydroxide, and then resulting solution was adjusted to pH 3.5 with 1M hydrochloric acid. After stirred in an ice bath for one hour, the resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give 3-methylsulfonylamino-6-methylthio-7-nitro-2(1H)-quinoxalinone (430 mg).

IR (KBr) : 1681, 1576, 1518, 1479, 1433, 1346, 1311, 1155, 968, 860 cm-1

1H NMR (DMSO-d_6, δ) : 2.57 (s, 3H), 3.42 (s, 3H), 7.65 (broad s, 1H), 8.08 (s, 1H), 11.3 (broad s, 1H), 12.69 (broad s, 1H)

FAB-MS (m/z) : 331 (MH^+)

mp : >280°C

Example 52

A suspension of 2-chloro-3-methylsulfonylamino-7-nitro-6-(pyridin-4-ylthio)quinoxaline (180 mg) in acetic acid (7.2 ml) was refluxed under nitrogen atmosphere for 90 minutes, and the resulting solution was cooled to 20°C. To the reaction mixture, cold water (50 ml) was added. The mixture was adjusted to pH 5 with 1M sodium hydroxide. After stirred in an ice bath for 30 minutes, the resulting precipitate was collected by filtration and washed with water and dried in vacuo to give 3-methylsulfonylamino-7-nitro-6-(pyridin-4-ylthio)-2(1H)-quinoxalinone (118 mg).

IR (KBr) : 1686, 1516, 1464, 1113 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.33 (s, 3H), 7.33 (d, J=5.7Hz, 2H), 7.65 (s, 1H), 7.98 (s, 1H), 8.45 (m, 2H)

APCI-MS (m/z) : 394 (MH^+)

mp : 269-271°C (decomp.)

Example 53

3-(3-Pyridylsulfonylamino)-6-fluoro-7-nitro-2(1H)-quinoxalinone was obtained according to substantially the similar manner to that of Example 52.

1H NMR (DMSO-d_6, δ) : 7.69 (dd, J=8.1, 4.8Hz, 1H), 7.80 (d, J=12.2Hz, 1H), 7.89 (d, J=7.2Hz, 1H), 8.55 (ddd, J=8.1, 2.1, 1.6Hz, 1H), 8.84 (dd, J=4.8, 1.6Hz, 1H), 9.24 (d, J=2.1Hz, 1H), 12.70 (broad s, 1H)

APCI-MS (m/z) : 366 (MH^+)

Example 54

To a stirred suspension of 3-methylsulfonylamino-6-methylthio-7-nitro-2(1H)-quinoxalinone (99 mg) in AcOH (3 ml) were added 1N-HCl (0.1 ml) and aqueous hydrogen peroxide (30%, 0.084 ml) at 5°C and the mixture was stirred at room temperature for 4 hours. The solution was diluted with IPE and the resulting precipitate was collected by filtration. The crude product was chromatographed on silica gel (gradient solution with AcOEt followed by AcOEt:AcOH = 30:1) to give 3-methylsulfonylamino-6-methylsulfonyl-7-nitro-2(1H)-quinoxalinone (24 mg).

1H NMR (DMSO-d_6, δ) : 2.88 (s, 3H), 3.40 (s, 3H), 8.12 (s, 1H), 8.16 (s, 1H), 12.87 (broad s, 1H)

FAB-MS (m/z) : 363 (MH^+)

Anal. Calcd for $C_{10}H_{10}N_4O_7S_2$:
C 33.15, H 2.78, N 15.46
Found : C 33.31, H 2.80, N 15.28

Example 55

6-(2-Imidazolylsulfonyl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone was obtained according to substantially the similar manner to that of Example 54.

1H NMR (DMSO-d_6, δ) : 3.46 (s, 3H), 7.17 (s, 2H), 8.17 (s, 1H), 8.35 (s, 1H), 13.07 (broad s, 1H)

FAB-MS (m/z) : 415 (MH^+)

Example 56

To a stirred suspension of 3-methylsulfonylamino-7-nitro-2(1H)-quinoxaline (4.5 g) in H_2O (317 ml) was added 0.1N-NaOH (158 ml) at 5°C and stirring was continued for 30 minutes at 5°C. After filtration, the filtrate was lyophilized to give sodium salt of 3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone (4.78 g).

IR (KBr) : 1672, 1522, 1471, 1336 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.02 (s, 3H), 7.27 (d, J=9.0Hz,

1H), 7.85 (d, J=2.7Hz, 1H), 7.90 (m, 1H), 11.86 (broad s, 1H)

APCI-MS (m/z) : 285 (MH^+) (free)

FAB-MS (m/z) : 307 (MH^+) (Na salt)

Example 57

Sodium salt of 6-(1-imidazolyl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone was obtained according to substantially the similar manner to that of Example 56.

IR (KBr) 1682, 1651, 1475 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.01 (s, 3H), 7.05 (m, 1H), 7.19 (s, 1H), 7.37 (m, 1H), 7.84 (m, 1H), 7.88 (s, 1H)

FAB-MS (m/z) : 373 (MH^+) (Na salt)

The following compounds (Examples 58 and 59) were obtained according to substantially the similar manner to that of Example 41.

Example 58

6-(2-Imidazolylthio)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone

1H NMR (DMSO-d_6, δ) : 3.28 (s, 3H), 6.74 (s, 1H), 7.41 (s, 2H), 8.07 (s, 1H), 12.72 (broad s, 1H)

FAB-MS (m/z) : 383 (MH^+)

Anal. Calcd for $C_{12}H_{10}N_6O_5S_2+1.2H_2O$:
C 35.68, H 3.09, N 20.80
Found : C 35.74, H 2.89, N 20.50

Example 59

2-Acetylamino-3-(3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone-6-yl-thio)propionic acid

1H NMR (DMSO-d_6, δ) : 1.84 (s, 3H), 3.33 (s, 3H), 3.59 (m, 2H), 4.46 (m, 1H), 7.67 (s, 1H), 7.80 (s, 1H), 8.44 (d, J=7.9Hz, 1H), 12.49 (broad s, 1H)

APCI-MS (m/z) : 446 (MH^+)

The following compounds (Examples 60 and 61) were obtained according to substantially the similar manner to that of Example 48.

Example 60

7,8,9,10-Tetrahydro-2-methylsulfonylamino-9-methyl-6-nitropyrido[3,4-f]-quinoxalin-3(4H)-one

1H NMR (DMSO-d_6, δ) : 3.01 (s, 3H), 3.31 (s, 3H), 3.38 (m, 2H), 3.46 (m, 2H), 4.59 (broad s, 2H), 7.90 (s, 1H)

FAB-MS (m/z) : 354 (MH^+)

Example 61

2-Methylsulfonylamino-6-nitropyrido[3,2-f]quinoxalin-3(4H)-one

1H NMR (DMSO-d_6, δ) : 3.54 (s, 3H), 7.86 (m, 1H), 8.11 (s, 1H), 9.00 (dd, J=3.5, 1.7Hz, 1H), 9.03 (m, 1H), 13.21 (broad s, 1H)

APCI-MS (m/z) : 336 (MH^+)

Preparation 86

A mixture of 2,3-diaminopyridine (15.08 g) and oxalic acid (24.85 g) in 4M hydrochloric acid (150 ml) was refluxed under nitrogen atmosphere for 4 hours and then cooled in an ice bath for 30 minutes. The resulting precipitate was collected by filtration and washed with water. The suspension of the precipitate in water (150 ml) was adjusted to pH 4.6 with 1M sodium hydroxide solution, and the resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give pyrido[2,3-b]pyrazine-2,3(1H,4H)-dione (17.57 g).

IR (KBr) : 1695, 1464, 1381 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.13 (dd, J=7.9, 4.8Hz, 1H), 7.46 (dd, J=7.9, 1.5Hz, 1H), 8.08 (dd, J=4.8, 1.5Hz, 1H), 11.97 (broad s, 1H), 12.31 (broad s, 1H)

APCI-MS (m/z) : 164 (MH^+)

mp : >280°C

Preparation 87

To a suspension of pyrido[2,3-b]pyrazine-2,3(1H,4H)-dione (4.89 g) in conc. sulfuric acid (49 ml) was added dropwise 60% nitric acid (d=1.38) (9.14 ml) at 0-10°C. After stirred at 80°C under nitrogen atmosphere for 24 hours, the resulting solution was poured into ice-water (300 ml), and the mixture was stirred in an ice bath for 30 minutes. The resulting preceipitate was collected by filtration and washed with water. A suspension of the precipitate in water (40 ml) was adjusted to pH 6 with 1M sodium hydroxide solution. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give 6,7-dinitropyrido-[2,3-b]pyrazine-2,3(1H,4H)-dione (3.32 g).

IR (KBr) : 1713, 1618, 1549, 1390, 1346, 845 cm^{-1}

1H NMR (DMSO-d_6, δ) : 8.12 (s, 1H), 12.58 (broad s, 1H), 13.29 (broad s, 1H)

mp : >280°C

Preparation 88

To a suspension of 6,7-dinitropyrido[2,3-b]pyrazine-2,3(1H,4H)-dione (2.53 g) in phosphorous oxychloride (25 ml) was added N,N-dimethylformamide (1.25 ml), and the mixture was refluxed under nitrogen atmosphere for 90 minutes. After cooled in an ice bath, the reaction mixture was poured into ice-water (125 ml). After adjustment to pH 5 with aqueous sodium hydroxide solution, the resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give 2,3-dichloro-6,7-dinitropyrido[2,3-b]pyrazine (4.97 g).

IR (KBr) : 1599, 1552, 1348, 1317, 1254, 1158, 1014 cm^{-1}

1H NMR ($CDCl_3$, δ) : 8.23 (s, 1H)

mp : 171-173°C

Preparation 89

To a suspension of sodium hydride (60% oil dispersion, 160 mg) in N,N-dimethylformamide (5.8 ml) was added methanesulfonamide (190 mg) at 0-5°C under nitrogen atmosphere, and the mixture was stirred at room temperature for 15 minutes. 2,3-Dichloro-6,7-dinitropyrido[2,3-b]-pyrazine (580 mg) was added to the mixture at 0-5°C, and the resulting solution was stirred at 0-5°C for 2 hours and then poured into a mixture of cold water (60 ml) and ethyl acetate (60 ml). The separated aqueous layer was adjusted to pH 4 with 1M hydrochloric acid and washed with ethyl acetate (60 ml). The aqueous layer was saturated with sodium chloride, and extracted with tetrahydrofuran (120 ml). The extract was washed with brine, dried over magnesium sulfate, and evaporated. The residue was triturated with n-hexane, and the resulting precipitate was collected by filtration, washed with n-hexane, and dried in vacuo to give 2-chloro-3-methylsulfonylamino-6,7-dinitropyrido[2,3-b]pyrazine (570 mg).

IR (KBr) : 1664, 1531, 1485, 1412, 1319, 1254, 1095, 939 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.06 (s, 3H), 8.74 (s, 1H)

mp : 236°C (decomp.)

Example 62

A suspension of 2-chloro-3-methylsulfonylamino-6,7-dinitropyrido[2,3-b]pyrazine (488 mg) in acetic acid (9.8 ml) was refluxed under nitrogen atmosphere for 2 hours, and the resulting solution was cooled to 20°C. To the reaction mixture, isopropyl ether (98 ml) was added. The resulting precipitate was collected by filtration and washed with isopropyl ether. The powder was dissolved in water at pH 8 with 1M sodium hydroxide solution, and adjusted to pH 2 with

1M hydrochloric acid under ice-cooling. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo to give 3-methylsulfonylamino-6,7-dinitropyrido[2,3-b]pyrazin-2(1H)-one (162 mg).

IR (KBr) : 1697, 1574, 1535, 1448, 1350, 1335, 1153, 1030, 972, 839 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.43 (s, 3H), 8.24 (s, 1H), 12.98 (broad s, 1H)

mp : 222°C

Example 63

According to the substantially the similar manner to that of Example 56, sodium salt of 3-methylsulfonylamino-7-nitro-6-(4-oxo-1,4-dihydropyridin-1-yl)-2(1H)-quinoxalinone was obtained.

IR (KBr) : 1684, 1643, 1556, 1518, 1504 cm^{-1}

1H NMR (DMSO-d_6, δ) : 3.02 (s, 3H), 6.15 (d, J=7.7Hz, 2H), 7.29 (s, 1H), 7.76 (d, J=7.7Hz, 2H), 7.93 (s, 1H), 11.96 (broad s, 1H)

The following compounds (Examples 64 and 65) were obtained according to substantially the similar manner to that of Example 41.

Example 64

6-(3-Bromo-4-oxo-1,4-dihydropyridin-1-yl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone

1H NMR (DMSO-d_6, δ) : 3.45 (s, 3H), 6.37 (m, 1H), 7.92-8.11 (m, 3H), 8.52 (m, 1H), 13.01 (broad s, 1H)

APCI-MS (m/z) : 456 (M^+)

Example 65

3-Methylsulfonylamino-7-nitro-6-(3-phenyl-4-oxo-1,4-dihydropyridin-1-yl)-2(1H)-quinoxalinone

1H NMR (DMSO-d_6, δ) : 3.43 (s, 3H), 6.34 (d, J=7.6Hz,

1H), 7.29-7.37 (m, 3H), 7.67 (m, 2H), 7.84 (dd, J=7.6, 2.4Hz, 1H), 8.07 (3H, m), 12.95 (broad s, 1H)

APCI-MS (m/z) : 454 (MH^+)

Preparation 90

To a suspension of 2-nitro-4-bromoaniline (0.2 g) and tetrakis(triphenylphosphine)palladium (53 mg) in toluene (15 ml) were added phenylboronic acid (0.17 g) and aqueous sodium carbonate (2M solution, 1.5 ml) and ethanol (4 ml). The resultant mixture was heated to reflux for 2 hours. After cooling to ambient temperature, the mixture was diluted with ethyl acetate (20 ml) and the organic layer was separated, which was washed in turn with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue which was chromatographed on silica gel (50 ml) eluting with a mixture of n-hexane and ethyl acetate (3% to 20%, V/V) to give 2-nitro-4-phenylaniline (0.17 g).

IR (KBr) : 3481, 3352, 1639, 1592, 1554, 1523, 1491 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.13 (d, J=8.8Hz, 1H), 7.23-7.70 (m, 7H), 7.79 (dd, J=8.8, 2.3Hz, 1H), 8.21 (d, J=2.3Hz, 1H)

APCI-MS (m/z) : 215 (MH^+)

Preparation 91

To a mixture of 2-nitro-4-phenylaniline (7.48 g) and triethylamine (12.1 ml) in N,N-dimethylformamide (80 ml) was added ethyl chloroglyoxylate (5.2 ml) at 5-15°C. After stirring at 5°C for 1 hour, the resultant mixture was taken up into a mixture of water (300 ml) and ethyl acetate (300 ml). The organic layer was separated, which was washed in turn with aqueous sodium hydrogen carbonate, hydrochloric acid (0.1N) and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a precipitate which was

collected by filtration and dried in vacuo to give N-ethoxalyl-2-nitro-4-phenylaniline (8.36 g).

IR (KBr) : 3311, 1718, 1577, 1529, 1493, 1444 cm^{-1}

1H NMR (DMSO-d_6, δ) : 1.34 (t, J=7.1Hz, 3H), 4.35 (q, J=7.1Hz, 2H), 7.35-7.60 (m, 3H), 7.70-7.90 (m, 2H), 8.08-8.22 (m, 2H), 8.34 (d, J=1.2Hz, 1H), 11.42 (s, 1H)

Preparation 92

To a mixture of titanium(III) chloride (c.a. 20% solution in hydrochloric acid, 100 ml) and water (58 ml) was added a suspension of N-ethoxalyl-2-nitro-4-phenylaniline (5.82 g) in acetone (175 ml) at 0-10°C. After stirring at ambient temperature for 3 hours, the resultant mixture was taken up into ice-water (800 ml). The resultant precipitate was collected by filtration, washed well with water, and dried in vacuo to give 6-phenyl-2,3(1H,4H)-quinoxalinedione (4.26 g).

IR (KBr) : 1720, 1670, 1612 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.21 (d, J=8.1Hz, 1H), 7.26-7.65 (m, 7H), 11.9 (s, 1H), 12.0 (s, 1H)

FAB-MS (m/z) : 239.1 (MH^+)

Preparation 93

To a solution of 6-phenyl-2,3(1H,4H)-quinoxalinedione (0.1 g) in conc. sulfuric acid (1 ml) was added potassium nitrate (43 mg) at -20°C. After stirring at -20°C for 30 minutes, the resultant mixture was taken up into ice-water (20 ml). After adjusting pH of the mixture to around 2 with aqueous ammonia (28%), the resultant precipitate was collected with filtration, washed well with water and dried in vacuo to give 7-nitro-6-(4-nitrophenyl)-2,3(1H,4H)-quinoxalinedione (91 mg).

IR (KBr) : 1720, 1693, 1398, 1342 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.08 (s, 1H), 7.62 (d, J=8.8Hz,

2H), 7.90 (s, 1H), 8.30 (d, J=8.8Hz, 2H), 12.26 (s, 1H), 12.37 (s, 1H)

APCI-MS (m/z)$^-$: 329 (MH^+)

Preparation 94

2,3-Dichloro-7-nitro-6-(4-nitrophenyl)quinoxaline (0.18 g) was obtained from 7-nitro-6-(4-nitrophenyl)-2,3(1H,4H)-quinoxalinedione (0.20 g) in substantially the same method as that of Preparation 16.

IR (KBr) : 1597, 1527, 1373, 1342, 1261, 1176, 1143 cm^{-1}

1H NMR (DMSO-d_6, δ) : 7.44 (d, J=8.3Hz, 2H), 7.72 (d, J=8.3Hz, 2H), 8.29 (s, 1H), 8.81 (s, 1H)

Preparation 95

2-Chloro-3-methylsulfonylamino-7-nitro-6-(4-nitrophenyl)quinoxaline (0.17 g) was obtained from 2,3-dichloro-7-nitro-6-(4-nitrophenyl)quinoxaline (0.20 g) and methanesulfonamide (52 mg) in substantially the same method as those of Preparations 22 to 24.

IR (KBr) : 1533, 1358, 1155 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.83 (s, 3H), 7.54 (d, J=8.4Hz, 2H), 7.87 (d, J=8.4Hz, 2H), 8.32 (s, 1H), 8.83 (s, 1H)

Example 66

3-Methylsulfonylamino-7-nitro-6-(4-nitrophenyl)-2-(1H)-quinoxalinone (144 mg) was obtained from 2-chloro-3-methylsulfonylamino-7-nitro-6-(4-nitrophenyl)quinoxaline (163 mg) in substantially the same method as that of Example 48.

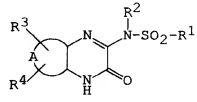
IR (KBr) : 1700, 1537, 1394, 1354 cm^{-1}

1H NMR (DMSO-d_6, δ) : 2.83 (s, 3H), 7.09 (s, 1H), 7.35 (d, J=8.3Hz, 2H), 7.80 (d, J=8.3Hz, 2H), 7.82 (s, 1H), 12.21 (s, 1H), 12.35 (s, 1H)

APCI-MS (m/z) : 406 (MH^+)

C L A I M S

1. A condensed heterocyclic compound of the following formula :



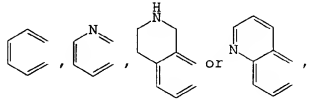
wherein R^1 is alkyl, halo(lower)alkyl, amino, aryl or heterocyclic group,

R^2 is hydrogen or lower alkyl,

R^3 and R^4 are each independently hydrogen, cyano, nitro, halogen, lower alkyl, halo(lower)alkyl, lower alkoxy, halo(lower)alkoxy, di(lower)alkylamino, aryl which may have one or more substituent(s), heterocyclic group which may have one or more substituent(s), lower alkylthio which may have one or more substituent(s), heterocyclicthio, lower alkylsulfonyl, lower alkylaminosulfonyl, or heterocyclicsulfonyl,

a group of the formula :

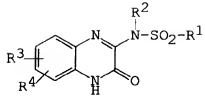
is the group of the formula :



and a salt thereof.

2. A compound of claim 1, wherein
R^1 is lower alkyl, higher alkyl, tri-halo(lower)alkyl, amino, phenyl, or unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),
R^2 is hydrogen or lower alkyl,
R^3 and R^4 are each independently hydrogen; cyano; nitro; halogen; lower alkyl; tri-halo(lower)alkyl; lower alkoxy, tri-halo(lower)alkoxy, di(lower)alkylamino; phenyl which may have 1 to 3 nitro; unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) or saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), each of which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, oxo, nitro, amino, pheny(lower)alkoxy which may have 1 to 3 lower alkoxy, hydroxy, halogen and phenyl; lower alkylthio which may have 1 to 3 substituent(s) selected from the group consisting of di(lower)alkylamino, protected amino and carboxy; heterocyclicthio, in which heterocyclic moiety is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s); lower alkylsulfonyl; lower alkylaminosulfonyl; or heterocyclicsulfonyl, in which heterocyclic moiety is unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s).

3. A compound of claim 2, which is the compound of the following formula :



wherein R^1, R^2, R^3 and R^4 are each as defined in claim 2,
and a salt thereof.

4. A compound of claim 3, wherein
R^1 is lower alkyl, higher alkyl, tri-halo(lower)alkyl, amino, phenyl, or pyridyl,
R^2 is hydrogen or lower alkyl,
R^3 and R^4 are each independently hydrogen; cyano; nitro; halogen; lower alkyl; tri-halo(lower)alkyl; lower alkoxy; tri-halo(lower)alkoxy; di(lower)alkylamino; phenyl which may have 1 to 3 nitro; imidazolyl, dihydropyridyl or piperazinyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, oxo, nitro, amino, phenyl(lower)alkoxy which may have 1 to 3 lower alkoxy, hydroxy, halogen and phenyl; lower alkylthio which may have 1 to 3 substituent(s) selected from the group consisting of di(lower)alkylamino, lower alkanoylamino and carboxy; pyridylthio; imidazolylthio; lower alkylsulfonyl; di(lower)alkylaminosulfonyl; or imidazolylsulfonyl.

5. A compound of claim 4, wherein
R^1 is lower alkyl,
R^2 is hydrogen,

R^3 is hydrogen, imidazolyl or dihydropyridyl having oxo, and

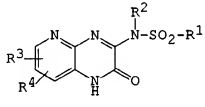
R^4 is nitro.

6. A compound of claim 5, which is 3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone, and its sodium salt.

7. A compound of claim 5, which is 6-(1-imidazolyl)-3-methylsulfonylamino-7-nitro-2(1H)-quinoxalinone, and its sodium salt.

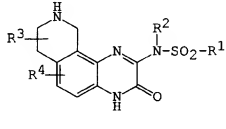
8. A compound of claim 5, which is 3-methylsulfonylamino-7-nitro-6-(4-oxo-1,4-dihydropyridin-1-yl)-2(1H)-quinoxalinone, and its sodium salt.

9. A compound of claim 2, which is the compound of the following formula :



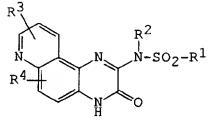
wherein R^1, R^2, R^3 and R^4 are each as defined in claim 2.

10. A compound of claim 2, which is the compound of the following formula :



wherein R^1, R^2, R^3 and R^4 are each as defined in claim 2.

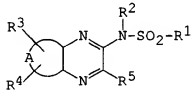
11. A compound of claim 2, which is the compound of the following formula :



wherein R^1, R^2, R^3 and R^4 are each as defined in claim 2.

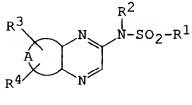
12. A process for the preparation of the compound of claim 1 or a salt thereof, which comprises

1) subjecting a compound of the formula :



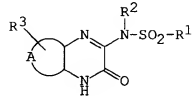
or a salt thereof, to conversion reaction of halogen to oxo, or

2) subjecting a compound of the formula :

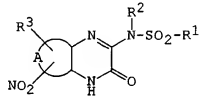


or a salt thereof, to introduction reaction of oxo, or

3) subjecting a compound of the formula :

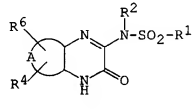


or a salt thereof, to nitration reaction, to give a compound of the formula :



or a salt thereof, or

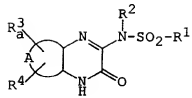
4) reacting a compound of the formula :



or a salt thereof, with a compound of the formula :

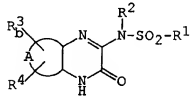
$$R_a^3\text{-}H$$

or a salt thereof, to give a compound of the formula :

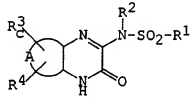


or a salt thereof, or

5) subjecting a compound of the formula :



or a salt thereof, to oxidation reaction, to give a compound of the formula :



or a salt thereof,

wherein R^1, R^2, R^3, R^4 and a group of the formula :

are each as defined in claim 1,

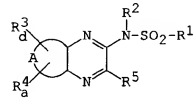
R^3_a is di(lower)alkylamino, N-containing heterocyclic group which may have one or more substituent(s), lower alkylthio which may have one or more substituent(s), or heterocyclicthio,

R^3_b is lower alkylthio or heterocyclicthio,

R^3_c is lower alkylsulfonyl or heterocyclicsulfonyl,

R^5 is halogen, and
R^6 is a leaving group.

13. A compound of the following formula :

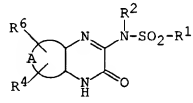


wherein R^1, R^2 and a group of the formula :

 are each as defined in claim 1,

R^3_d and R^4_a are each independently hydrogen, nitro or halogen, and
R^5 is halogen,
or a salt thereof.

14. A compound of the following formula :



wherein R^1, R^2, R^4 and a group of the formula :

 are each as defined in claim 1, and

R^6 is a leaving group,
and a salt thereof.

15. A pharmaceutical composition which comprises, as an active ingredient, a condensed heterocyclic compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

16. Use of a condensed heterocyclic compound of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

17. A condensed heterocyclic compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

18. A method for the prevention and/or the treatment of anxiety, depression, schizophrenia, epilepsy, cognition disorders, stroke, cerebral ischemia, head trauma, spinal cord trauma, cardiac arrest, hypoglycemia, anoxia, convulsion, brain edema, Alzheimer's disease, Huntington's chorea, Parkinson's disease, and opiate tolerance and withdrawal, which comprises administering a condensed heterocyclic compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

INTERNATIONAL SEARCH REPORT

Inten nal Application No
PCT/JP 97/00571

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D241/44 C07D403/04 C07D403/14 C07D403/12 C07D487/04
A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 118, no. 21, 24 May 1993 Columbus, Ohio, US; abstract no. 213023b, S. J. HAYS ET. AL.: "N-Sulfonyl derivatives of 6,7-dichloro-3,4-dihydro-3-oxo-quinoxalinecarboxylate as glycine site NMDA and AMPA antagonists." page 913; column 1; XP002031762 see abstract & BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 3, no. 1, 1993, pages 77-80, --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 May 1997	20.06.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Helps, I

Form PCT/ISA/210 (second sheet) (July 1992)

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 24, 25 November 1994, WASHINGTON DC, US, pages 4053-67, XP002031761 P. D. LEESON ET. AL.: "The Glycine Site on the NMDA Receptor: Structure-Activity Relationships and Therapeutic Potential. " see whole document, especially page 4059, figure 7 ---	1-18
A	WO 95 12417 A (ACEA PHARMACEUTICALS) 11 May 1995 see claims; examples ---	1-18
A	WO 95 18616 A (ACEA PHARMACEUTICALS) 13 July 1995 see claims; examples ---	1-18
A	EP 0 676 397 A (SHIONOGI & CO. LTD.) 11 October 1995 see claims; examples -----	1-18

1

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP 97/00571

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 18
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/JP 97/00571

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9512417 A	11-05-95	US 5514680 A	07-05-96
		AU 1172395 A	23-05-95
		CA 2175795 A	11-05-95
		EP 0732942 A	25-09-96
		FI 961858 A	04-07-96
		NO 961770 A	05-07-96
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		US 5622952 A	22-04-97
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		CA 2146478 A	09-10-95
		CN 1123792 A	05-06-96
		HU 72064 A	28-03-96
		JP 7324084 A	12-12-95
		ZA 9502841 A	18-12-95